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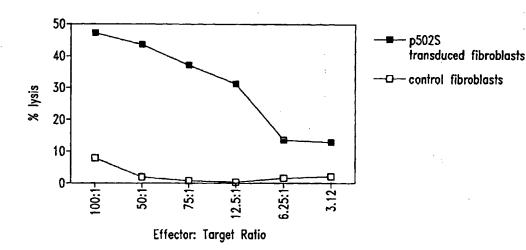
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### (54) Title: COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.



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# COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

### **TECHNICAL FIELD**

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

### BACKGROUND OF THE INVENTION

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating

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such cancers. The present invention fulfills these needs and further provides other related advantages.

### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and (c) complements of any of the sequence of (a) or (b). In certain specific embodiments, such a polypeptide comprises at least a portion, or variant thereof, of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount

detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

## BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate tumor polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate tumor polypeptide P502S. In each case, the number of γ-interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate tumor polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate tumor antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferongamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

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SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16

SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1

SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9

SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4

SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17

SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17

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SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862

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SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19

SEO ID NO: 17 is the determined 5' cDNA sequence for J1-19

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SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55
SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858
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SEQ ID NO: 108 is the predicted amino acid sequence for F1-12
SEO ID NO: 109 is the determined full length cDNA sequence for J1-17
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SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772 SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309 SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-4288 SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283 SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304 SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296 SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280 SEO ID NO: 207 is the determined cDNA sequence for 10-d8fwd SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con SEO ID NO: 209 is the determined cDNA sequence for 11-C8rev SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd SEO ID NO: 211 is the determined cDNA sequence for 7.g6rev SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev SEO ID NO: 216 is the determined cDNA sequence for 8-d4fwd SEO ID NO: 217 is the determined cDNA sequence for 8-d9rev SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev SEQ ID NO: 223 is the determined cDNA sequence for P509S SEO ID NO: 224 is the determined cDNA sequence for P510S SEQ ID NO: 225 is the determined cDNA sequence for P703DE5 SEO ID NO: 226 is the determined cDNA sequence for 9-A11 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6 SEO ID NO: 228 is the determined cDNA sequence for 8-H7

SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13 SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14 SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24 SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25 SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30 SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34 SEQ ID NO: 236 is the determined cDNA sequence for PTPN35 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36 SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38 SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39 SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40 SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42 SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45 SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46 SEO ID NO: 245 is the determined cDNA sequence for JPTPN51 SEO ID NO: 246 is the determined cDNA sequence for JPTPN56 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64 SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65 SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67 SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76 SEO ID NO: 251 is the determined cDNA sequence for JPTPN84 SEO ID NO: 252 is the determined cDNA sequence for JPTPN85 SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86 SEO ID NO: 254 is the determined cDNA sequence for JPTPN87 SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88 SEQ ID NO: 256 is the determined cDNA sequence for JP1F1 SEO ID NO: 257 is the determined cDNA sequence for JP1F2 SEQ ID NO: 258 is the determined cDNA sequence for JP1C2

SEQ ID NO: 259 is the determined cDNA sequence for JP1B1 SEQ ID NO: 260 is the determined cDNA sequence for JP1B2 SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEO ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEO ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEO ID NO: 272 is the determined cDNA sequence for JP1A9 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEO ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6

SEQ ID NO: 289 is the determined cDNA sequence for JP8F5 SEQ ID NO: 290 is the determined cDNA sequence for JP8A8 SEQ ID NO: 291 is the determined cDNA sequence for JP8C7 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7 SEQ ID NO: 293 is the determined cDNA sequence for P8D8 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7 SEQ ID NO: 295 is the determined cDNA sequence for JP8F8 SEQ ID NO: 296 is the determined cDNA sequence for JP8G8 SEO ID NO: 297 is the determined cDNA sequence for JP8B10 SEQ ID NO: 298 is the determined cDNA sequence for JP8C10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9 SEQ ID NO: 300 is the determined cDNA sequence for JP8E10 SEQ ID NO: 301 is the determined cDNA sequence for JP8F9 SEO ID NO: 302 is the determined cDNA sequence for JP8H9 SEQ ID NO: 303 is the determined cDNA sequence for JP8C12 SEO ID NO: 304 is the determined cDNA sequence for JP8E11 SEQ ID NO: 305 is the determined cDNA sequence for JP8E12 SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12 SEO ID NO: 307 is the determined cDNA sequence for P711P SEQ ID NO: 308 is the determined cDNA sequence for P712P SEQ ID NO: 309 is the determined cDNA sequence for CLONE23 SEO ID NO: 310 is the determined cDNA sequence for P774P SEQ ID NO: 311 is the determined cDNA sequence for P775P SEO ID NO: 312 is the determined cDNA sequence for P715P SEQ ID NO: 313 is the determined cDNA sequence for P710P SEQ ID NO: 314 is the determined cDNA sequence for P767P SEQ ID NO: 315 is the determined cDNA sequence for P768P SEO ID NO: 316-325 are the determined cDNA sequences of previously isolated genes SEO ID NO: 326 is the determined cDNA sequence for P703PDE5 SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5

SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26

SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26

SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23

SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23

SEQ ID NO: 332 is the determined full length cDNA sequence for P509S

SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred

to as 11-C9)

SEQ ID NO: 334 is the determined cDNA sequence for P714P

SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-

F3)

SEQ ID NO: 336 is the predicted amino acid sequence for P705P

SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

SEQ ID NO: 338 is the amino acid sequence of the peptide p5

SEQ ID NO: 339 is the predicted amino acid sequence of P509S

SEQ ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P

SEQ ID NO: 342 is the determined cDNA sequence for P789P

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to

Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to

Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to

Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to

Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to

Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to

Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to

Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of

B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 375.

SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553.

SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

- SEQ ID NO:411 is the cDNA sequence for 22567.
- SEQ ID NO:412 is the cDNA sequence for 22568.
- SEQ ID NO:413 is the cDNA sequence for 22570.
- SEQ ID NO:414 is the cDNA sequence for 22571.
- SEQ ID NO:415 is the cDNA sequence for 22572.
- SEQ ID NO:416 is the cDNA sequence for 22573.
- SEQ ID NO:417 is the cDNA sequence for 22573.
- SEQ ID NO:418 is the cDNA sequence for 22575.
- SEQ ID NO:419 is the cDNA sequence for 22580.
- SEO ID NO:420 is the cDNA sequence for 22581.
- SEQ ID NO:421 is the cDNA sequence for 22582.
- SEO ID NO:422 is the cDNA sequence for 22583.
- SEQ ID NO:423 is the cDNA sequence for 22584.
- SEQ ID NO:424 is the cDNA sequence for 22585.
- SEQ ID NO:425 is the cDNA sequence for 22586.
- SEQ ID NO:426 is the cDNA sequence for 22587.
- SEQ ID NO:427 is the cDNA sequence for 22588.
- SEQ ID NO:428 is the cDNA sequence for 22589.
- SEO ID NO:429 is the cDNA sequence for 22590.
- SEQ ID NO:430 is the cDNA sequence for 22591.
- SEQ ID NO:431 is the cDNA sequence for 22592.
- SEQ ID NO:432 is the cDNA sequence for 22593.
- SEQ ID NO:433 is the cDNA sequence for 22594.
- SEQ ID NO:434 is the cDNA sequence for 22595.
- SEQ ID NO:435 is the cDNA sequence for 22596.
- SEQ ID NO:436 is the cDNA sequence for 22847.
- SEQ ID NO:437 is the cDNA sequence for 22848.
- SEQ ID NO:438 is the cDNA sequence for 22849.
- SEO ID NO:439 is the cDNA sequence for 22851.
- SEQ ID NO:440 is the cDNA sequence for 22852.

- SEQ ID NO:441 is the cDNA sequence for 22853.
- SEQ ID NO:442 is the cDNA sequence for 22854.
- SEQ ID NO:443 is the cDNA sequence for 22855.
- SEQ ID NO:444 is the cDNA sequence for 22856.
- SEQ ID NO:445 is the cDNA sequence for 22857.
- SEQ ID NO:446 is the cDNA sequence for 23601.
- SEQ ID NO:447 is the cDNA sequence for 23602.
- SEQ ID NO:448 is the cDNA sequence for 23605.
- SEQ ID NO:449 is the cDNA sequence for 23606.
- SEQ ID NO:450 is the cDNA sequence for 23612.
- SEQ ID NO:451 is the cDNA sequence for 23614.
- SEQ ID NO:452 is the cDNA sequence for 23618.
- SEQ ID NO:453 is the cDNA sequence for 23622.
- SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
- SEQ ID NO:455 is the cDNA sequence for LIM protein.
- SEQ ID NO:456 is the cDNA sequence for a known gene.
- SEQ ID NO:457 is the cDNA sequence for a known gene.
- SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
- SEO ID NO:459 is the cDNA sequence for 23045.
- SEQ ID NO:460 is the cDNA sequence for 23032.
- SEQ ID NO:461 is the cDNA sequence for 23054.
- SEQ ID NOs:462-467 are cDNA sequences for known genes.
- SEQ ID NOs:468-471 are cDNA sequences for P710P.
- SEQ ID NO:472 is a cDNA sequence for P1001C.
- SEQ ID NO:473 is the amino acid sequence for PSMA.
- SEQ ID NO:474 is the amino acid sequence for PAP.
- SEQ ID NO:475 is the amino acid sequence for PSA.
- SEQ ID NO:476 is the amino acid sequence for a fusion protein containing PSA, P703P and P501S.

### DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer. The compositions described herein may include prostate tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a prostate tumor protein or a variant thereof. A "prostate tumor protein" is a protein that is expressed in prostate tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain prostate tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a Antibodies are generally immune system proteins, or antigen-binding sequence. fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human prostate tumor proteins. Sequences of polynucleotides encoding certain tumor proteins, or portions thereof, are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Sequences of polypeptides comprising at least a portion of a tumor protein are provided in SEQ ID NOs:112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

### PROSTATE TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a prostate tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a prostate tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a prostate tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a prostate tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native prostate tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions,

usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy* – the Principles and *Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are

capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native prostate tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a prostate tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Other methods employing amplification may also be Res. 19:3055-60, 1991). employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding at least a portion of a prostate tumor protein are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Isolation of these polynucleotides is described below. Each of these prostate tumor proteins was overexpressed in prostate tumor tissue.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may

also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a prostate tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a prostate tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, *Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

### PROSTATE TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a prostate tumor protein or a variant thereof, as described herein. As noted above, a "prostate tumor protein" is a protein that is expressed by prostate tumor cells. Proteins that are prostate tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera

and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigenspecific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most

preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression

vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be

targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

In certain embodiments, the present invention provides fusion proteins comprising a polypeptide disclosed herein together with at least one of the following known prostate antigens: prostate specific antigen (PSA); prostatic acid phosphatase (PAP); and prostate specific membrane antigen (PSMA). The protein sequences for PSMA, PAP and PSA are provided in SEQ ID NO: 473-475, respectively. In certain embodiments, the fusion proteins of the present invention comprise PSA, PAP and/or PSMA in combination with one or more of the following the inventive antigens: P501S (amino acid sequence provided in SEQ ID NO: 113); P703P (amino acid sequences provided in SEQ ID NO: 327, 329, 331); P704P (cDNA sequence provided in SEQ ID NO: 67): P712P (cDNA sequence provided in SEO ID NO: 308); P775P (cDNA sequence provided in SEQ ID NO: 311); P776P (cDNA sequence provided in SEQ ID NO: 354); P790P (cDNA sequence provided in SEQ ID NO: 352). The amino acid sequence of a fusion protein of PSA, P703P and P501S is provided in SEQ ID NO: 476. In preferred embodiments, the inventive fusion proteins comprise one of the following combinations of antigens: PSA and P703P; PSA and P501S; PAP and P703P; PAP and P501S; PSMA and P703P; PSMA and P501S; PSA, PAP and P703P; PSA, PAP and P501S: PSA, PAP, PSMA and P703P, PSA, PAP, PSMA and P501S. One of skill in the art will appreciate that the order of polypeptides within a fusion protein can be altered without substantially changing the therapeutic, prophylactic or diagnostic properties of the fusion protein.

The fusion proteins described above are more immunogenic and will be effective in a greater number of prostate cancer patients than any of the individual components alone. The use of multiple antigens in the form of a fusion protein also lessens the likelihood of immunologic escape.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide

components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-

terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

#### BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal

indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested

c.

by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

#### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (*see also* U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate tumor polypeptide, polynucleotide encoding a prostate tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively,

detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8+. Prostate tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

### PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions

or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner

et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be

formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically polysaccharides; polyphosphazenes; biodegradable derivatized microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt.

MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific

immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4:*594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into

dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a prostate tumor protein (or portion or other variant thereof) such that the prostate tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting. cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be

pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

#### **CANCER THERAPY**

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth in vitro, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccinedependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-In general, for pharmaceutical compositions and vaccines vaccinated patients. comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 ug to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from

the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991), at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a prostate tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with prostate tumor polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a prostate tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%,

preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375 and 381. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter

performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

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#### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate tumor protein in a biological sample. Such kits generally comprise

at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate tumor protein.

The following Examples are offered by way of illustration and not by way of . limitation.

#### **EXAMPLES**

#### **EXAMPLE 1**

## ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A+ RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A+ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the Notl/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/Notl site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones

having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 μg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μl of H<sub>2</sub>O, heat-denatured and mixed with 100 μl (100 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax E.

coli DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12. This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the

driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to nonhuman sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193,

respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be overexpressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339.

# EXAMPLE 2 DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate tumor polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42  $^{0}$ C for one hour. The cDNA was then amplified by PCR with genespecific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-

expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis et al. (Proc. Natl. Acad. Sci. USA 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive

cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

### **EXAMPLE 3**

### ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to

previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor

compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor

and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both microarray technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively.

The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted

amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

### EXAMPLE 4 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

### **EXAMPLE 5**

## • FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were

separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig

valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be overexpressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be

expressed in small intestine. Of the 26 clones, 10 (SEQ ID NO: 340-349) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350-365.

### EXAMPLE 6

### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2.1 (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-Ab binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 106 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 106/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, Science 258:815-818, 1992) and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x  $10^4$  cells/ well) as stimulators and A2 transgenic spleen cells

as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2.1 expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2.1 molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2.1 were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg

of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

# EXAMPLE 7 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE TUMOR POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed in vitro to the P2S-12 peptide (SEO ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (Critical Reviews in Immunology 18:65-75, 1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a γ-interferon ELISPOT assay (see Lalvani et al., J. Exp. Med. 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 10<sup>4</sup> fibroblasts in the presence of 3 μg/ml human β<sub>2</sub>microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml y-interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a  $\gamma$ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of y-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of yinterferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

### **EXAMPLE 8**

## PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate tumor antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg VR10132-P501S either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed A2-restricted CTL epitope.

#### **EXAMPLE 9**

# GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE TUMOR ANTIGEN

Using *in vitro* whole-gene priming with P501S-retrovirally transduced autologous fibroblasts (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched fibroblast lines transduced with P501S, these CTL lines were shown to be restricted HLA-A2 class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured

overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S-transduced autologous fibroblasts. The P501S-specific activity could be sustained by the continued stimulation of the cultures with P501S-transduced fibroblasts in the presence of IL-15. A panel of HLA-mismatched fibroblast lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be restricted by HLA-A2. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

### **EXAMPLE 10**

# IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE TUMOR ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2 transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of P703P transduced target cells expressing either HLA-A2Kb or HLA-A2. Specifically, HLA-A2 transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* 

stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with p5 peptide and cultured with GM-CSF and IL-4 together with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated.

#### EXAMPLE 11

## EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate tumor and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach).

### **EXAMPLE 12**

## ELICITATION OF PROSTATE TUMOR ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate tumor antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8+ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-The P501S-specific activity of cell line 3A-1 could be transduced fibroblasts. maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxity assays (51Cr release) and interferon-gamma production (Interferon-gamma Elispot; see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

# EXAMPLE 13 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang(23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		`\
TEEG		,

CGI-82 showed 4.06 fold over-expression in prostate tissues as

compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal The expression of this gene in normal tissues was very low. prostate tissues. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of

normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

# EXAMPLE 14 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate tumor antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped

(aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups, Plus (normal prostate and prostate tumor libraries, and breast cell lines, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

<u>Table II</u>

<u>Prostate cDNA Libraries and ESTs</u>

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones found in the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones found in the Plus, Minus and Other group libraries, but the

expression in the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones found in Plus, Minus and Other group libraries, but the expression in the Plus group is higher than the expression in the Minus group. This analysis identified 4,345 breast clusters (*see* Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III
Prostate Cluster Summary

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (i.e., the level in prostate tumor cDNA was at least three times the level in normal prostate cDNA) were

identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NOs:401-453, with certain novel sequences shown in SEQ ID NOs:407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u>

<u>Prostate-tumor Specific Clones</u>

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P

433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57
439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

# EXAMPLE 15 FURTHER IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NOs:454-467. Of these sequences SEQ ID NOs:459-461 correspond to novel genes. The others (SEQ ID NOs:454-458 and 461-467) correspond to known sequences.

### **EXAMPLE 16**

### FURTHER CHARACTERIZATION OF PROSTATE TUMOR ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic ABI Sequencer. Four sequences were obtained, and are presented in SEQ ID NOs:468-471.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

#### **CLAIMS**

- 1. An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472;
- (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and
  - (c) complements of any of the sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 339 and 383.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate tumor protein, or a variant thereof that differs in one or more

substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.

- 5. An isolated polynucleotide encoding a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 7. An isolated polynucleotide comprising a sequence that hybridizes, under moderately stringent conditions, to a sequence recited in any one of

SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.

- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims 4-7.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An expression vector comprising a polynucleotide according claim 8.
- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- 13. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
- 14. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 15. A vaccine according to claim 14, wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine according to claim 14, wherein the non-specific immune response enhancer induces a predominantly Type I response.

- 17. A pharmaceutical composition comprising a polynucleotide according to claim 4, in combination with a physiologically acceptable carrier.
- 18. A vaccine comprising a polynucleotide according to claim 4, in combination with a non-specific immune response enhancer.
- 19. A vaccine according to claim 18, wherein the non-specific immune response enhancer is an adjuvant.
- 20. A vaccine according to claim 18, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 21. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472 or a complement of any of the foregoing polynucleotide sequences.
- 22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 26. A vaccine according to claim 25, wherein the non-specific immune response enhancer is an adjuvant.
- 27. A vaccine according to claim 25, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-

binding fragment thereof according to claim 21, and thereby inhibiting the development of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is prostate cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.

40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.

- 41. A vaccine comprising a fusion protein according to claim 35, in combination with a non-specific immune response enhancer.
- 42. A vaccine according to claim 41, wherein the non-specific immune response enhancer is an adjuvant.
- 43. A vaccine according to claim 41, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with a non-specific immune response enhancer.
- 46. A vaccine according to claim 45, wherein the non-specific immune response enhancer is an adjuvant.
- 47. A vaccine according to claim 45, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.

49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.

- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the prostate tumor protein from the sample.

- 51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.
- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and/or

(iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.
- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

- (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate;

- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

59. A method according to claim 58, wherein the binding agent is an antibody.

- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.
- 61. A method according to claim 58, wherein the cancer is prostate cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.

65. A method according to claim 62, wherein the cancer is a prostate cancer.

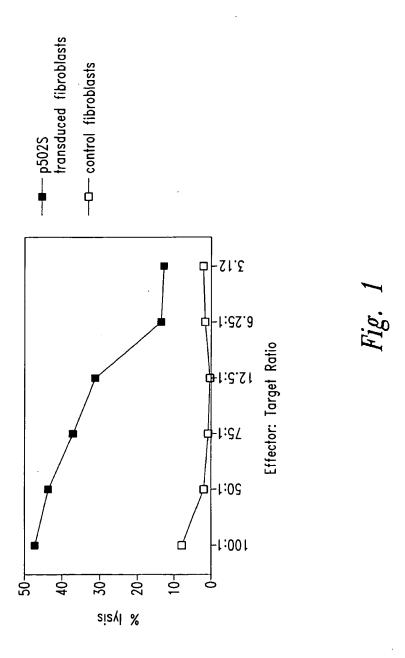
- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor

protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;

- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 72. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 21; and
  - (b) a detection reagent comprising a reporter group.
- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.

75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotides.
- 78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
  - 79. A diagnostic kit, comprising:
  - (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.



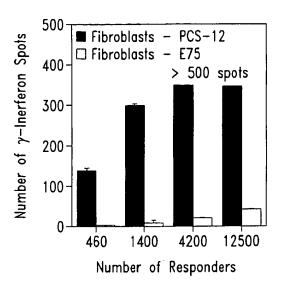


Fig. 2A

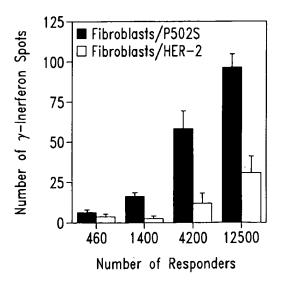
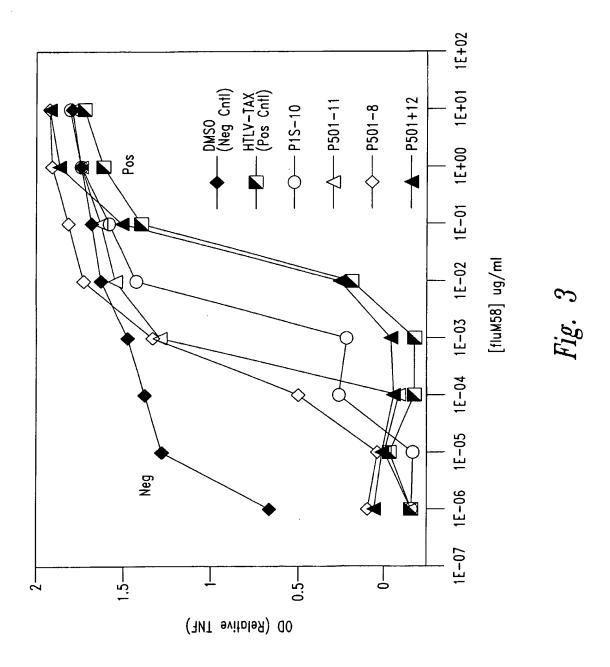
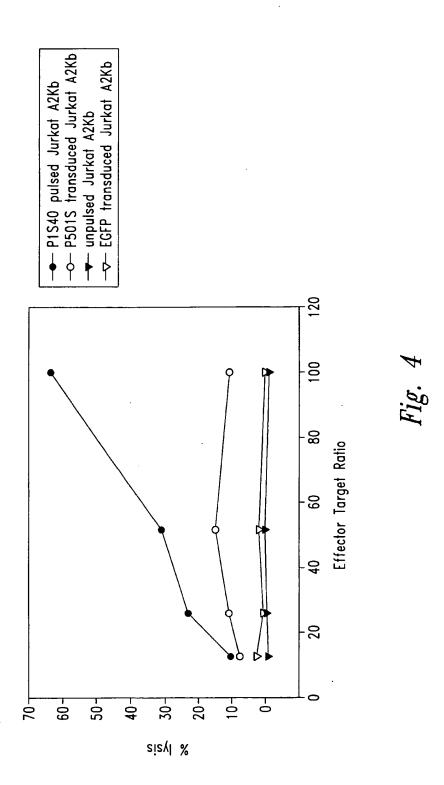
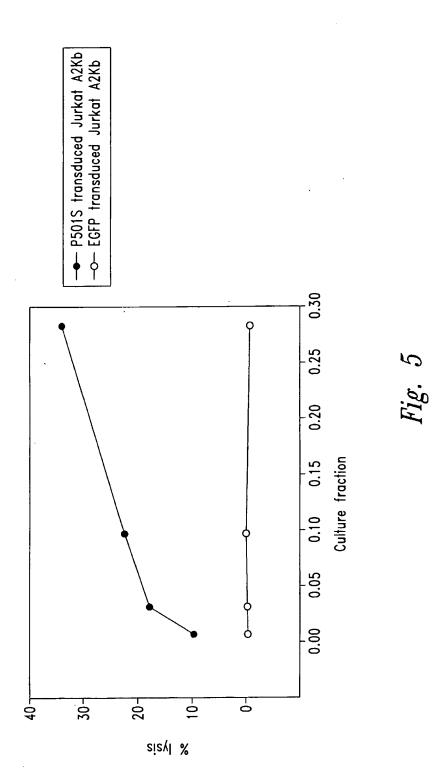


Fig. 2B







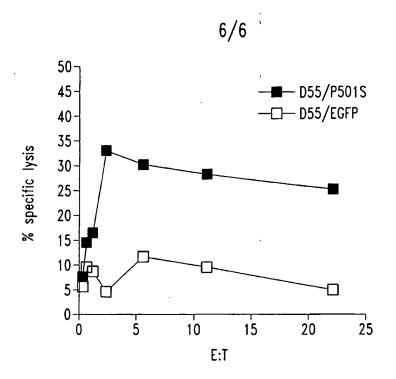
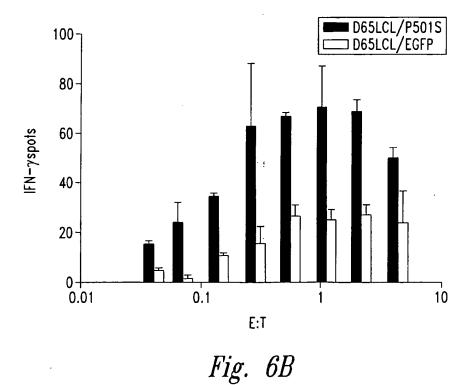


Fig. 6A



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ttttttttt tttttcacag tataacagct ctttatttct gtgagttcta ctaggaaatc
                                                                           60
atcaaatctg agggttgtct ggaggacttc aatacacctc cccccatagt gaatcagctt
                                                                          120
ccagggggtc cagtecetet cettacttea tecceatece atgecaaagg aagaceetee
                                                                          180
ctecttaget cacaqeette tetaggette ceagtqeete caggacagag tgggttatgt
                                                                          240
tttcagctcc atcettgctg tgagtgtctg gtgcgttgtg cctccagctt ctgctcagtg cttcatggac agtgtccagc acatgtcact ctccactctc tcagtgtgga tccactagtt
                                                                          300
                                                                          360
ctagagegge egecacegeg gtggagetee agettttgtt ecetttagtg agggttaatt
                                                                          420
qcqcqcttqq cqtaatcatq gtcataactq tttcctgtgt gaaattgtta tccgctcaca
                                                                          480
attocacaca acatacgago oggaagcata aagtgtaaag ootggggtgo otaatgagtg
                                                                          540
anctaactca cattaattgc gttgcgctca ctgnccgctt tccagtcngg aaaactgtcg
                                                                          600
                                                                          660
tgccagctgc attaatgaat cggccaacgc ncggggaaaa gcggtttgcg ttttgggggc
                                                                          720
tetteegett etegeteact nanteetgeg eteggtentt eggetgeggg gaacggtate
actoctoaaa ggnggtatta cggttatoon naaatonggg gataccongg aaaaaanttt
                                                                          780
                                                                          814
aacaaaaggg cancaaaggg cngaaacgta aaaa
      <210> 2
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (816)
      <223> n = A, T, C \text{ or } G
acagaaatgt tggatggtgg agcacctttc tatacgactt acaggacagc agatggggaa
                                                                           60
                                                                          120
ttcatqqctq ttqqaqcaat aqaaccccaq ttctacqaqc tqctqatcaa aqqacttgga
                                                                          180
ctaaagtctg atgaacttcc caatcagatg agcatggatg attggccaga aatgaagaag
aagtttgcag atgtatttgc aaagaagacg aaggcagagt ggtgtcaaat ctttgacggc
                                                                          240
acagatgeet gtgtgactee ggttetgaet tttgaggagg ttgtteatea tgateacaae
                                                                          300
aaggaacggg gctcgtttat caccagtgag gagcaggacg tgagcccccg ccctgcacct
                                                                          360
ctgctgttaa acaccccaqc catccttct ttcaaaaqqq atccactagt tctagaagcg
                                                                          420
gccgccaccg cggtggagct ccagcttttg ttccctttag tgagggttaa ttgcgcgctt
                                                                          480
```

```
ggcgtaatca tggtcatagc tgtttcctqt qtqaaattqt tatccqctca caattccccc
                                                                           540
aacatacgag coggaacata aagtgttaag cotggggtgc ctaatgantg agctaacton
                                                                           600
cattaattqc qttgcqctca ctgcccgctt tccagtcggg aaaactgtcg tgccactgcn
                                                                           660
ttantgaatc ngccacccc cgggaaaagg cggttgcntt ttgggcctct tccqctttcc
                                                                           720
tegeteattg atectngene eeggtetteg getgeggnga aeggtteact ceteaaagge
                                                                           780
ggtntnccgg ttatccccaa acnggggata cccnga
                                                                           816
       <210> 3
       <211> 773
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (773)
       <223> n = A, T, C or G
       <400> 3
cttttgaaag aagggatggc tggggtgttt aacagcagag gtgcagggcg ggggctcacg
                                                                            60
tcctgctcct cactggtgat aaacgagccc cgttccttgt tgtgatcatg atgaacaacc
                                                                           120
tcctcaaaag tcagaaccgg agtcacacag gcatctgtgc cqtcaaagat ttgacaccac
                                                                           180
totgoottog tottotttgc aaatacatot gcaaacttot tottoattto tggocaatca
                                                                           240
tecatgetea tetgattggg aagtteatea gaetttagte cannteettt gateageage
                                                                           300
tegtagaact ggggttetat tgeteeaaca gecatgaatt ecceatetge tgteetgtaa
                                                                           360
gtcgtataga aaggtgetee accatecaae atgttetgte etegaggggg ggeeeggtae ceaattegee etatantgag tegtattaeg egegeteaet ggeegtegtt ttacaaegte
                                                                           420
                                                                           480
gtgactggga aaaccctggg cgttaccaac ttaatcgcct tgcagcacat ccccctttcg
                                                                           540
ccagctgggc gtaatancga aaaggcccgc accgatcgcc cttccaacag ttgcqcacct
                                                                           600
gaatgggnaa atgggacccc cctgttaccg cgcattnaac ccccgcnqqq tttnqttqtt
                                                                           660
acceccaent nnacegetta caetttgeca gegeettane gecegeteee ttteneettt
                                                                           720
cttcccttcc tttcncnccn ctttcccccg gggtttcccc cntcaaaccc cna
                                                                           773
      <210> 4
      <211> 828
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(828)
      <223> n = A, T, C or G
cctcctgagt cctactgacc tgtgctttct ggtgtggagt ccagggctgc taggaaaagg
                                                                            60
aatgggcaga cacaggtgta tgccaatgtt tctgaaatgg gtataatttc gtcctctct
                                                                           120
teggaacact ggetgtetet gaagaettet egeteagttt eagtgaggae acacacaaag
                                                                           180
acgtgggtga ccatgttgtt tgtggggtgc agagatggga ggggtggggc ccaccctgga
                                                                           240
agagtggaca gtgacacaag gtggacactc totacagatc actgaggata agctggagcc acaatgcatg aggcacacac acagcaagga tgacnotgta aacatagcoc acgctgtoot
                                                                           300
                                                                           360
gngggcactg ggaagcctan atnaggccgt gagcanaaaq aaqqqqaqqa tccactaqtt
                                                                           420
ctanagegge egecacegeg gtgganetee anettttgtt ecetttagtg agggttaatt
                                                                           480
gcgcgcttgg cntaatcatg gtcatanctn tttcctgtgt gaaattgtta tccgctcaca
                                                                           540.
attecacaca acatacgane eggaaacata aantgtaaac etggggtgee taatgantga
                                                                           600
ctaactcaca ttaattgcgt tgcgctcact gcccgctttc caatcnggaa acctgtcttg
                                                                           660
concttgcat tnatgaatcn gccaaccccc ggggaaaagc gtttgcgttt tgggcgctct
                                                                           720
teegetteet eneteantta nteetnene teggteatte eggetgenge aaaceggtte
                                                                           780
accncctcca aagggggtat tccggtttcc ccnaatccgg gganancc
                                                                           828
      <210> 5
      <211> 834
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc_feature
      <222> (1) ... (834)
      <223> n = A, T, C or G
      <400> 5
ttttttttt tttttactga tagatggaat ttattaagct tttcacatgt gatagcacat
                                                                          60
agttttaatt gcatccaaag tactaacaaa aactctagca atcaagaatg gcagcatgtt
                                                                         120
attttataac aatcaacacc tgtggctttt aaaatttggt tttcataaga taatttatac
                                                                         180
tqaaqtaaat ctaqccatqc ttttaaaaaa tqctttaqqt cactccaaqc ttqqcaqtta
                                                                         240
acatttggca taaacaataa taaaacaatc acaatttaat aaataacaaa tacaacattg
                                                                         300
taggccataa tcatatacag tataaggaaa aggtggtagt gttgagtaag cagttattag
                                                                         360
aataqaatac cttqqcctct atqcaaatat qtctaqacac tttqattcac tcaqcctqa
                                                                         420
                                                                         480
cattcagttt tcaaagtagg agacaggttc tacagtatca ttttacagtt tccaacacat
                                                                         540
tgaaaacaag tagaaaatga tgagttgatt tttattaatg cattacatcc tcaagagtta
tcaccaaccc ctcagttata aaaaattttc aagttatatt agtcatataa cttggtgtgc
                                                                         600
ttattttaaa ttagtgctaa atggattaag tgaagacaac aatggtcccc taatgtgatt
                                                                         660
gatattggtc atttttacca gcttctaaat ctnaactttc aggcttttga actggaacat
                                                                         720
tgnatnacag tgttccanag ttncaaccta ctggaacatt acagtgtgct tgattcaaaa
                                                                         780
                                                                         834
tgttattttg ttaaaaatta aattttaacc tggtggaaaa ataatttgaa atna
      <210> 6
      <211> 818
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(818)
      <223> n = A, T, C or G
      <400> 6
ttttttttt tttttttt aagaccctca tcaatagatg gagacataca gaaatagtca
                                                                          60
                                                                         120
aaccacatct acaaaatgcc agtatcaggc ggcggcttcg aagccaaagt gatgtttgga
                                                                         180
tgtaaagtga aatattagtt ggcggatgaa gcagatagtg aggaaagttg agccaataat
gacgtgaagt ccgtggaagc ctgtggctac aaaaaatgtt gagccgtaga tgccgtcqqa
                                                                         240
aatqqtqaaq qgagactcga agtactctga ggcttgtagg agggtaaaat agagacccag
                                                                         300
taaaattgta ataagcagtg cttgaattat ttggtttcgg ttgttttcta ttagactatg
                                                                         360
gtgageteag gtgattgata eteetgatge gagtaataeg gatgtgttta ggagtgggae teetagggga tttagegggg tgatgeetgt tgggggeeag tgeeeteeta gttggggggt
                                                                         420
                                                                         480
aggggctagg ctggagtggt aaaaggctca gaaaaatcct gcgaagaaaa aaacttctga
                                                                         540
ggtaataaat aggattatcc cgtatcgaag gcctttttgg acaggtggtg tgtggtggcc
                                                                         600
                                                                         660
ttqqtatqtq ctttctcqtq ttacatcqcq ccatcattqq tatatqqtta qtqtgttggg
ttantanggo ctantatgaa gaacttttgg antggaatta aatcaatngo ttggccggaa
                                                                         720
gtcattanga nggctnaaaa ggccctgtta ngggtctggg ctnggtttta cccnacccat
                                                                         780
                                                                         818
ggaatnence ecceggaena ntgnatecet attettaa
      <210> 7
      <211> 817
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(817)
      <223> n = A, T, C or G
      <400> 7
                                                                          60
ttttttttt tttttttt tggctctaga gggggtagag ggggtgctat agggtaaata
                                                                         120
cqqqcctat ttcaaaqatt tttaqqqqaa ttaattctaq qacqatqqqt atgaaactgt
                                                                         180
ggtttgctcc acagatttca gagcattgac cgtagtatac ccccggtcgt gtagcggtga
```

```
aagtggtttg gtttagacgt ccgggaattg catctgtttt taagcctaat gtggggacag
                                                                         240
ctcatgagtg caagacgtct tgtgatgtaa ttattatacn aatgggggct tcaatcggga
                                                                         300
gtactactcg attgtcaacg tcaaggagtc gcaggtcgcc tggttctagg aataatgqqq
                                                                         360
gaagtatgta ggaattgaag attaatccgc cgtagtcggt gttctcctag gttcaatacc
                                                                         420
attggtggcc aattgatttg atggtaaggg gagggatcgt tgaactcgtc tgttatgtaa
                                                                         480
aggatncctt ngggatggga aggcnatnaa ggactangga tnaatggcgg gcangatatt
                                                                         540
tcaaacngtc tctanttcct gaaacqtctq aaatqttaat aanaattaan tttngttatt
                                                                         600
gaatnttnng gaaaagggct tacaggacta gaaaccaaat angaaaanta atnntaangg
                                                                         660
cnttatentn aaaggtnata aceneteeta tnateeeace caatngnatt ecceaenenn
                                                                         720
acnattggat necessantte canaaangge enceeeegg tgnanneene ettttgttee
                                                                         780
cttnantgan ggttattene ecetngentt atcance
                                                                         817
       <210> 8
       <211> 799
      <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(799)
      <223> n = A, T, C \text{ or } G
catttccggg tttactttct aaggaaagcc gagcggaagc tqctaacqtq qqaatcqqtq
                                                                          60
cataaggaga actttctgct ggcacgcgct agggacaagc gggagagcga ctccgagcgt
                                                                         120
ctgaagcgca cgtcccagaa ggtggacttg gcactgaaac agctgggaca catccgcgag
                                                                         180
tacgaacage geetgaaagt getggagegg gaggteeage agtgtageeg egteetgggg
                                                                         240
tgggtggccg angectgane egetetgeet tgetgeeece angtgggeeg ceaececetg
                                                                         300
acctgcctgg gtccaaacac tgagccctgc tggcggactt caagganaac ccccacangg
                                                                         360
ggattttgct cctanantaa ggctcatctg ggcctcggcc ccccacctg gttggccttg tctttgangt gagccccatg tccatctggg ccactgtcng gaccaccttt ngggagtgtt
                                                                         420
                                                                         480
cteettacaa ecacannatg eceggeteet eceggaaace anteceance tongaaggat
                                                                         540
caagneetgn atceactnnt netanaaceg geeneeneeg engtggaace eneettntgt
                                                                         600
teettttent tnagggttaa tnnegeettg geettneean ngteetnene ntttteennt
                                                                         660
gttnaaattg ttangeneec neennteeen ennennenan eeegaeeenn annttnnann
                                                                         720
nectgggggt neennengat tgacconnec neeetntant tgenttnggg nnenntgeec
                                                                         780
ctttccctct nggganncg
                                                                         799
      <210> 9
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (801)
      <223> n = A, T, C or G
acgccttgat cctcccaggc tgggactggt tctgggagga gccgggcatg ctgtggtttg
                                                                          60
taangatgac actcccaaag gtggtcctga cagtggccca gatggacatg gggctcacct
                                                                         120
caaggacaag gccaccaggt gcgggggccg aagcccacat gatccttact ctatgagcaa
                                                                         180
aatcccctgt gggggcttct ccttgaagtc cgccancagg gctcagtctt tggacccang
                                                                         24.0
caggicatgg ggitgingne caactggggg ceneaacgca aaanggenea gggeetengn
                                                                         300
cacccatcce angacgegge tacactnetg gacetecene tecaccaett teatgegetg
                                                                         360`
ttentaceeg egnatntgte eeanetgttt engtgeenae teeanettet nggaegtgeg
                                                                         420
ctacatacgc ccggantcnc nctcccgctt tgtccctatc cacgtnccan caacaaattt
                                                                         480
encentantg cacenattee caenttinne agnitteene nnegngette etintaaaag
                                                                         540
ggttganccc cggaaaatnc cccaaagggg gggggccngg tacccaactn ccccctnata
                                                                         600
gctgaantcc ccatnaccnn gnctcnatgg ancentcent tttaannacn ttctnaactt
                                                                         660
gggaanance etegneenth ecceenttaa teceneettg enangnment ecceenntee
                                                                         720
necennntng gentntnann enaaaaagge eennnaneaa teteetnnen eeteantteg
                                                                         780
```

```
ccancecteg aaateggeen e
                                                                         801
       <210> 10
       <211> 789
       <212> DNA
       <213> Homo sapien
       <221> misc feature
       <222> (1) ... (789)
       <223> n = A, T, C or G
       <400> 10
 cagtctatnt ggccagtgtg gcagctttcc ctgtggctgc cggtgccaca tgcctgtccc
                                                                          60
 acagtqtqqc cqtqqtqaca qcttcaqccq ccctcaccqq qttcaccttc tcagccctqc
                                                                         120
                                                                         180
 agatectgee etacacactg geeteeetet accaeeggga gaageaggtg tteetgeeea
                                                                         240
 aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc
 caqqccctaa qcctqqaqct cccttcccta atggacacgt gggtgctgga ggcagtggcc
                                                                         300
 tgeteceace tecacegeg etetgegggg cetetgeetg tgatgtetee gtacgtgtgg
                                                                         360
                                                                         420
 tggtgggtga gcccaccgan gccagggtgg ttccgggccg gggcatctgc ctggacctcg
                                                                         480
 ccatcctgga tagtgcttcc tgctgtccca ngtggcccca tccctgttta tgggctccat
 tgtccagctc agccagtctg tcactgccta tatggtgtct gccgcaggcc tgggtctggt
                                                                         540
 cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcagcg
                                                                         600
 ttaaaaaatt ccaqcaacat tqqqqqtqqa aqqcctqcct cactgggtcc aactccccgc
                                                                         660
 tcctgttaac cccatggggc tgccggcttg gccgccaatt tctgttgctg ccaaantnat
                                                                         720
 gtggctctct gctgccacct gttgctggct gaagtgcnta cngcncanct nggggggtng
                                                                         780
                                                                         789
gangttccc
       <210> 11
<211> 772
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(772)
       \langle 223 \rangle n = A, T, C or G
       <400> 11
 cccacctac ccaaatatta gacaccaaca cagaaaagct agcaatggat tcccttctac
 tttqttaaat aaataaqtta aatatttaaa tqcctqtqtc tctqtgatgg caacagaagg
                                                                         120
                                                                         180
 accaacaggc cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc
 tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata
                                                                         240
 actiticatat qttcaaatcc catggaggag tqtttcatcc tagaaactcc catgcaagag
                                                                         300
                                                                         360
 ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt
 tattcagete ccaaaaacce ttetetaggt gtgteteaac taggaggeta getgttaace
                                                                         420
 ctgagcctgg gtaatccacc tgcagagtcc ccgcattcca gtgcatggaa cccttctggc
                                                                         480
 ctcctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana
                                                                         540
 aactggggaa aaaagaaaag gacgcccan ccccagctg tgcanctacg cacctcaaca
                                                                         600
                                                                         660
 qcacaqqqtq qcaqcaaaaa aaccacttta ctttqqcaca aacaaaaact ngggggggca
 accceggeac ecenangggg gttaacagga anengggnaa entggaacec aattnaggea
                                                                         720
                                                                         772
 ggcccnccac cccnaatntt gctgggaaat ttttcctccc ctaaattntt tc
       <210> 12
       <211> 751
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(751)
       <223> n = A, T, C or G
```

```
<400> 12
gccccaattc cagetgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                          60
agctgattga agcaaccete tactttttgg tegtgageet tttgettggt geaggtttea
                                                                         120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                         180
aagtanggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                         240
atggtggtgt tocacacttg agtgaagtot tootgggaac cataatottt ottgatggca
                                                                         300
ggcactacca gcaacgtcag ggaagtgctc agccattgtg gtgtacacca aggcgaccac
                                                                         360
agcagetgen accteageaa tgaagatgan gaggangatg aagaagaacg tenegaggge
                                                                         420
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna
                                                                         480
cnccggctgc gatgaagaaa tnaccccncg ttgacaaact tgcatggcac tggganccac
                                                                         540
agtggcccna aaaatcttca aaaaggatgc cccatcnatt gaccccccaa atgcccactg
                                                                         600
ccaacagggg ctgccccacn cncnnaacga tganccnatt gnacaagatc tncntggtct
                                                                         660
tnatnaacht gaaccetgen tngtggetee tgtteaggne ennggeetga ettetnaann
                                                                         720
aangaacton gaagnoocca enggananne g
                                                                         751
      <210> 13
      <211> 729
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(729)
      <223> n = A,T,C or G
      <400> 13
gagecaggeg tecetetgee tgeecactea gtggeaacae eegggagetg ttttqteett
                                                                          60
tgtggancet cagcagtnee etettteaga aeteantgee aaganeeetg aacaggagee
                                                                         120
accatgcagt getteagett cattaagace atgatgatee tetteaattt geteatettt
                                                                         180
ctgtgtggtg cagccctgtt ggcagtgggc atctgggtgt caatcgatgg ggcatccttt
                                                                         240
ctgaagatct tcgggccact gtcgtccagt gccatgcagt ttgtcaacgt gggctacttc
                                                                         300
ctcatcgcag ccggcgttgt ggtcttagct ctaggtttcc tgggctgcta tggtgctaag
                                                                         360
actgagagea agtgtgccct cgtgacgttc ttcttcatcc tcctcctcat cttcattqct
                                                                         420
gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt
                                                                         480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt
                                                                         540
gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacqqatttt
                                                                         600
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa
                                                                         660
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa
                                                                         720
attnaaggg
                                                                         729
      <210> 14
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(816)
      <223> n = A, T, C \text{ or } G
      <400> 14
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcgcag
                                                                          60
tgttcgctga aggggttgta gtaccagcgc gggatgctct ccttgcagag tcctgtgtct
                                                                         120
ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcgtcaaag ccactcgtgt atttttcaca ggcagcctcg tccgacgcgt cggggcagtt gggggtgtct
                                                                         180
                                                                         240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga
                                                                         300
cangiged ageacactgg atggegett tecatgnnan gggeetgng ggaaagtee
                                                                         360
tganccccan anctgcctct caaangcccc accttgcaca ccccgacagg ctagaatgga
                                                                         420
atcttcttcc cgaaaggtag ttnttcttgt tgcccaancc anccccntaa acaaactctt
                                                                         480
gcanatotgo toognggggg tentantaco anogtgggaa aagaacocca ggengegaac
                                                                         540
caancttgtt tggatnegaa genataatet netnttetge ttggtggaca geaceantna
                                                                         600
```

```
\verb|ctgtnnanct|| \verb|ttagnccntg|| \verb|gtctcntgg|| \verb|gttgnncttg|| \verb|aacctaatcn|| \verb|ccnntcaact||
                                                                           660
qqqacaaqqt aantnqccnt cctttnaatt cccnancntn ccccctggtt tggggttttn
                                                                           720
                                                                           780
cnenctecta ecceaquaan neegtqttee ecceeaacta qqqqeenaaa cennttntte
                                                                           816
cacaaccetn ccccacccac gggttcngnt ggttng
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (783)
      <223> n = A,T,C \text{ or } G
      <400> 15
                                                                            60
ccaaggcctg ggcaggcata nacttgaagg tacaacccca ggaacccctg gtgctgaagg
atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagagga
                                                                           120
                                                                           180
aaqacccaaa ccaqqtqqaa ctqtqqqqac tcaaggaang cacctacctg ttccagctga
cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca
                                                                           240
ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                           300
                                                                           360
teccaeqetq qtactatgae eccaeggage agatetgeaa gagtttegtt tatggagget
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg
                                                                           420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                           480
                                                                           540
ncaatggctg ctgcatcnac antttcctng aattgtgaca acacccccca ntgcccccaa
                                                                           600
ccctcccaac aaaqcttccc tqttnaaaaa tacnccantt ggcttttnac aaacncccgg
                                                                           660
                                                                           720
cnecteentt tteecenntn aacaaagge netngenttt gaaetgeeen aaccenggaa
                                                                           780
tetneenngg aaaaantnee eeceetget eetnnaance eeteenenaa anetneeeee
                                                                           783
ccc
      <210> 16
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(801)
      <223> n = A, T, C or G
      <400> 16
                                                                            60
qccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                           120
agetgattga ageaaccete taetttttgg tegtgageet tttgettggt geaggtttea
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                           180
                                                                           240
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
atggtggtgt tocacacttg agtgaagtot toctgggaac cataatottt cttgatggca
                                                                           300
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca
                                                                           360
                                                                           420
qcaqctqcaa cctcaqcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
cacttgetet cegtettage accatageag eccangaaac caagageaaa gaccacaacg
                                                                           480
                                                                           540
congctgcga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt
                                                                           600
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
                                                                           660
cnacaggget geneenenen gaaagaatga gecattgaag aaggatente ntggtettaa
tqaactqaaa contqoatqq tqqoocotqt tcaqqqotot tqqcaqtqaa ttotqanaaa
                                                                           720
                                                                           780
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc
                                                                           801
ggccaaggan ccctgccccn g
      <210> 17
      <211> 740
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc_feature
      <222> (1) ... (740)
      <223> n = A, T, C or G
      <400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccqqqa qctgttttgt
                                                                          60
cctttgtgga gcctcagcag ttccctcttt cagaactcac tqccaaqaqc cctqaacaqq
                                                                         120
agccaccatg cagtgettea getteattaa gaccatgatg atcetettea attigeteat
                                                                         180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                         240
cttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta cttcctcatc gcagccggcg ttgtggtctt tgctcttggt ttcctgggct gctatggtgc
                                                                         300
                                                                         360
taagacggag agcaagtgtg coctogtgac gitcttcttc atcctcctcc tcatcttcat
                                                                         420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct
                                                                         480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc
                                                                         540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg
                                                                         600
gaattttgaa aganteneec taetteeaaa aaaaaanant tgeetttnee eeenttetgt
                                                                         660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                         720
caaaaaaant nnaagggttn
                                                                         740
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (802)
      <223> n = A, T, C or G
      <400> 18
ccgctggttg cgctggtcca gngnagccac gaagcacgtc agcatacaca qcctcaatca
                                                                          60
caaggtette cagetgeege acattaegea gggeaagage etecageaac actgeatatg
                                                                         120
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct
                                                                         180
gagcetetgt tagtggagga agatteeggg etteagetaa gtagteageg tatqteecat
                                                                         240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                         300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                         360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                         420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                         480
gctcaggatg tccagagacg tgqttccqcc ccctcnctta atqacaccqn ccanncaacc
                                                                         540
gtcggctccc gccgantgng ttcgtcgtnc ctgggtcagg gtctgctggc cnctacttgc
                                                                         600
aancttegte nggeecatgg aatteacene aeeggaactn gtangateea etnnttetat
                                                                         660
aaccggncgc caccgcnnnt ggaactccac tetinttnec titacttqaq qqttaaqqtc
                                                                         720
accettnneg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                         780
tnecancene atangaagee ng
                                                                         802
      <210> 19
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (731)
      <223> n = A, T, C or G
      <400> 19
cnaagettee aggtnacggg cegenaance tgaccenagg tancanaang cagnengegg
                                                                          60
gageccaceg teacgnggng gngtetttat nggagggge ggagecacat enetggaent
                                                                         120
entgacecca acteceence neneantgea gtgatgagtg cagaactgaa ggtnacgtgg
                                                                         180
caggaaccaa gancaaanne tgeteennte caagteggen nagggggegg ggetggeeac
                                                                         240
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                         300
```

```
360
catgeccagn gttanataac nggengagag tnantttgec tetecettee ggetgegean
                                                                       420
cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccncccct
                                                                       480
ccactaagct cagaacaaaa aacttegaca ccactcantt gtcacctgnc tgctcaagta
                                                                       540
aagtgtaccc catnoccaat gtntgctnga ngctctgncc tgcnttangt tcggtcctgg
                                                                       600
gaagacetat caattnaage tatgtttetg actgeetett geteeetgna acaanenace
cnncnntcca aggggggnc ggccccaat cccccaacc ntnaattnan tttanccccn
                                                                       660
cccccnggcc cggcctttta cnancntcnn nnacngggna aaaccnnngc tttncccaac
                                                                       720
                                                                       731
nnaatccncc t
      <210> 20
      <211> 754
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(754)
      <223> n = A, T, C or G
      <400> 20
ttttttttt tttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc
                                                                       120
caaccccctc ntccaaatnn ccntttccgg gngggggttc caaacccaan ttanntttgg
                                                                       180
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                       240
tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccg
aaatnqttna nqqaaaaccc aanttctcnt aaqqttqttt qaaqqntnaa tnaaaanccc
                                                                       300
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa
                                                                       360
qqnnanccc qqttantnaa tcccccnnc cccaattata ccqanttttt ttngaattgg
                                                                       420
                                                                       480
gancconegg gaattaacgg ggnnnntccc tnttgggggg enggnnecec eccenteggg
                                                                       540
ggttngggnc aggnennaat tgtttaaggg teegaaaaat eeeteenaga aaaaaanete
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
                                                                       600
qqqqcctqqq attttntttc ccctnttncc tccccccc ccnggganag aggttngngt
                                                                       660
                                                                       720
tttgntcnnc ggcccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga
agtccnttgn agggntaaan ggccccctnn cggg
                                                                       754
      <210> 21
      <211> 755
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(755)
     <223> n = A, T, C or G
                                                                        60
atcancecat gacceenaac nngggacene teanceggne nnnenacene eggeenatea
nngtnagnne actnennttn nateaeneee encenactae gecenenane enaegeneta
                                                                       120
nncanatnee actganngeg egangtngan ngagaaanet nataccanag neaccanaen
                                                                       180
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattn
                                                                       240
nncnncanat gattttcctn anccgattac contneccec tanccectec eccecaacna
                                                                       300
cqaaqqenet qqnccnaaqq nnqcqncncc ccqctaqntc cccnncaaqt cncncnccta
                                                                       360
aactcancen nattacnege ttentgagta teactceecg aateteacee tactcaacte
                                                                       420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt
                                                                       480
ttagnggtee ntnaanente etaataette eagtetneet tenecaattt eenaangget
                                                                       540
ctttengaca gcatnttttg gttecenntt gggttettan ngaattgeee ttentngaac
                                                                      600
aggetentet titeettegg trancetggn trenneegge eagtrattat trecentitt
                                                                      660
aaattenine entitantit tggenttena aaceeegge ettgaaaaeg geeeeetggt
                                                                      720
                                                                      755
aaaaggttgt tttganaaaa tttttgtttt gttcc
     <210> 22
     <211> 849
     <212> DNA
```

```
<213> Homo sapien
       <220>
      <221> misc_feature
      <222> (1) ... (849)
      <223> n = A, T, C \text{ or } G
      <400> 22
ttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt
                                                                           60
acgetnggan taangegace eganttetag ganneneet aaaateanae tqtqaaqatn
                                                                          120
atcetgnnna eggaanggte aceggnngat nntgetaggg tgncenetee cannnenttn
                                                                          180
cataacteng nggccctgcc caccaccttc ggcggcccng ngnccgggcc cgggtcattn
                                                                          240
gnnttaaccn cactnngcna neggttteen neecenneng accenggega teeggggtne
                                                                          300
totgtottoc cotgnagnon anaaantggg concggnooc otttaccoot nnacaagcca
                                                                          360
engeenteta neenengeee ecectecant nngggggaet geenannget eegttnetng
                                                                          420
nnaccconnn gggtncctcg gttgtcgant cnaccgnang ccanggattc cnaaggaagg
                                                                          480
tgcgttnttg gcccctaccc ttcgctncgg nncacccttc ccgacnanga nccqctcccq
                                                                          540
chenneghing cetenceteg caacaceege netentengt neggninece ecceaceege
                                                                          600
necetenene ngnegnanen eteeneenee gteteannea eeaceegee eegeeaggee
                                                                          660
ntcanccacn ggnngacnng nagenennte geneegegen gegneneett egeenengaa
                                                                          720
ctnentengg ceantnnege teaancenna enaaaegeeg etgegeggee eqnagegnee
                                                                          780
necteenega gteeteeegn etteenacee angnntteen egaggaeaen nnaceeegee
                                                                          840
nncangcgg
                                                                          849
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(872)
      <223> n = A, T, C or G
      <400> 23
gcgcaaacta tacttcgctc gnactcgtgc gcctcgctnc tcttttcctc cgcaaccatg
                                                                           60
tetgaenane eegattngge ngatatenan aagntegane agteeaaaet gantaacaca
                                                                          120
cacachenan aganaaatee netgeettee anaqtanaen attqaachnq agaaccange
                                                                          180
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccagcntcnc
                                                                          240
ctnccnaccc tacntcttcn nagctgtcnn acccetngtn cqnacceccc naggteggga
                                                                          300
tegggtttnn nntgacegng ennecettee eccenteeat nacganeene eegeaceaee
                                                                          360
nanngenege necegnnet ettegeenee etgteetntn eeeetgtnge etggenengn
                                                                          420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                          480
tgggnnngcg tctgcnccgc gttccttccn ncnncttcca ccatcttcnt tacngggtct
                                                                          540
concgeente tennneaene cetgggaege thteethtge ecceetthae tecceeett
                                                                          600
cgncqtqncc cgnccccacc ntcatttnca nacgntcttc acaannncct ggntnnctcc
                                                                          660
chanchgnen gteaneenag ggaagggngg ggnneenntg nttgaegttg nggngangte egaanantee teneentean enetaeeeet egggegnnet etengttnee aaettaneaa
                                                                         720
                                                                         780
ntetecceg ngngemente teagectene concecenet etetgeantg tnetetgete
                                                                         840
tnaccnntac gantnttcgn cnccctcttt cc
                                                                         872
      <210> 24
      <211> 815
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(815)
      <223> n = A, T, C or G
      <400> 24
```

```
gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta
                                                                              .60
 nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta
                                                                             120
 tentneatta gtaacaantg tnntgteeat cetqtengan canatteeca tnnattnegn
                                                                             180
 cgcattenen geneantatn taatnqqqaa ntennntnnn neacenneat etatentnee
                                                                             240
 gcnccctgac tggnagagat ggatnanttc tnntntgacc nacatgttca tcttggattn
                                                                             300
 aananceece egengneeae eggttngnng enageennte eeaagaeete etgtggaggt
                                                                             360
 aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaagt ngnnncanan
                                                                             420
 gatcccgtcc aggnttnacc atccttcnc agggcccct ttngtqcctt anagnqnagc
                                                                             480
 gtgtccnanc enetcaacat ganacgegee agneeanceg caattnggea caatgtegne
                                                                             540
 gaacccccta gggggantna tncaaanccc caggattqtc cncncanqaa atcccncanc
                                                                             600
cccnccctac ccnnctttgg gacngtgacc aantcccgga gtnccagtcc ggccngnctc
                                                                             660
 ccccaccggt nnccntgggg gggtgaanct cngnntcanc cngncgaggn ntcgnaagga
                                                                             720
accggneetn ggnegaanng anenntenga agngeenent eqtataacce ecceteneca
                                                                             780
ncenacngnt agntccccc engggtnegg aangg
                                                                             815
       <210> 25
       <211> 775
       <212> DNA
       <213> Homo sapien
       <221> misc feature
       <222> (1) ... (775)
       <223> n = A, T, C or G
       <400> 25
ccgagatgtc tcgctccgtg gccttagctg tgctcgcgct actctctctt tctggcctgg
                                                                              60
aggetateca gegtaeteca aagatteagg titaeteacg teatecagea gagaatggaa
                                                                             120
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgact
                                                                             180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                             240
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                             300
                                                                             360
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt
                                                                             420
etgettgett genttttaat antgatatge ntatacacce taccetttat gnececaaat
                                                                             480
tgtaggggtt acatnantgt tenentngga catgatette etttataant cencentteg
                                                                             540
aattgcccgt enccengttn ngaatgttte ennaaceaeg gttggeteee eeaggtenee
                                                                             600
tettaeggaa gggeetggge enetttneaa ggttggggga acenaaaatt tenettntge eeneceneea enntettgng nneneanttt ggaaceette enatteeeet tggeetenna
                                                                             660
                                                                             720
nccttnncta anaaaacttn aaancgtngc naaanntttn acttcccccc ttacc
                                                                             775
      <210> 26
       <211> 820
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
       <222> (1) ... (820)
      \langle 223 \rangle n = A, T, C or G
      <400> 26
anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
cccanagata nettatanca acagtgettt gaccaagage tgetgggeae attteetgea
                                                                             120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                             180
ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca ntgatgacca tgggcgggag cgagcctctt ccctgnaccg gggtggcana nganagccta
                                                                             240
                                                                             300
nctgaggggt cacactataa acgttaacga conagatnan cacctgcttc aagtgcaccc
                                                                             360
ttcctacctg acnaccagng accnnnaact gengeetggg gacagenetg ggancageta
                                                                             420
acnnageact cacetgeece eccatggeeg thegenteec tggteetqne aagggaaget
                                                                             480
ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                            540
gatggaattt thecetteeg geennteece tetteettta caeqeeceet nntactente
                                                                             600
tecetetntt nteetgnene aettttnace cennnattte eettnattga teggannetn
                                                                             660
```

```
ganattccac tnncgcctnc cntcnatcng naanacnaaa nactntctna cccnggggat
                                                                          720
gggnnecteg nteatectet etttttenet acencenntt etttgeetet eettngatea
780tccaacente gntggeentn ecceecennn teetttneee
820
       <210> 27
       <211> 818
       <212> DNA
       <213> Homo sapien
       <220>
      <221> misc feature
       <222> (1)...(818)
       <223> n = A, T, C or G
       <400> 27
totgggtgat ggcctcttcc tcctcaggga cctctgactg ctctgggcca aagaatctct
                                                                           60
tgtttcttct ccgagcccca ggcagcggtg attcagccct gcccaacctg attctgatga
                                                                          120
ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                          180
ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct gggctgggtc
                                                                          240
teegecteca gggttetget etteeangea ngceancaag tggegetggg ceacactgge ttetteetge ecentecetg getetgante tetgtettee tgteetgtge angeneettg
                                                                          300
                                                                          360
gatctcagtt tecetenete anngaactet gtttetgann tetteantta actntgantt
                                                                          420
tatnacenan tggnetgtne tgtennactt taatgggeen gaeeggetaa teeeteete
                                                                          480
nctcccttcc anttcnnnna accngcttnc cntcntctcc ccntancccg ccngggaanc
                                                                          540
ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggcnng gtnnctncnc
                                                                          600
etgntnncec enetenennt theetegtee ennennegen nngeanntte nengteeenn
                                                                          660
tnnctcttcn ngtntcgnaa ngntcncntn tnnnnngncn ngntnntncn tccctctcnc
                                                                          720
ennntgnang tnnttnnnne nengnneece nnnnennnnn nggnnntnnn tetnenenge
                                                                          780
cccnnccccc ngnattaagg cctccnntct ccggccnc
                                                                          818
      <210> 28
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (731)
      <223> n = A, T, C \text{ or } G
      <400> 28
aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg
                                                                           60
toccaacatg anggtgnngt totottttga angagggttg ngtttttann conggtgggt
                                                                          120
gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcagtat
                                                                          180
ntanatteet gtnaategga aaatnatntt tennenggaa aatnttgete eeateegnaa
                                                                          240
attnetcccg ggtagtgcat nttngggggn cngccangtt tcccaggctq ctanaatcqt
                                                                          300
actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatcon tacccgactg
                                                                          360
tnnnttncct tegecetntg actetgenng ageceaatae cenngngnat gtenecengn
                                                                          420
nnngcgnene tgaaannnne tegnggetnn gancateang gggtttegea teaaaagenn
                                                                          480
egitteneat naaggeactt ingesteate caaceneing eestennesa titingeegie
                                                                          540
nggttenect acgetnning encetnnin ganatitine eegeeinggg naanceteet
                                                                          600
gnaatgggta gggnettnte ttttnacenn gnggtntact aatennetne acgentnett
                                                                          660
tetenacece eccettttt caateecane ggenaatggg gteteecenn eganggggg
                                                                          720
nnncccannc c
                                                                          731
      <210> 29
      <211> 822
      <212> DNA
      <213> Homo sapien
      <220>
```

. !

```
<221> misc_feature
      <222> (1) ... (822)
      <223> n = A, T, C or G
      <400> 29
actaqtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat
                                                                       120
cqctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncnnt
atnintacne teatanneet ennnaceeae teeetettaa eeentactgi geetaingen -
                                                                       180
thnetantet ntgeegeeth enanceacen gtgggeenac enenngnatt etenatetee
                                                                       240
                                                                       300
tenecatntn geetananta ngtneatace etatacetae necaatgeta nnnetaanen
                                                                       360
tocatnantt annntaacta ccactgacnt ngactttone atnanctoct aatttgaate
tactctgact cccacngcct annuattagc ancutccccc nacnatutct caaccaaatc
                                                                       420
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aacccccctc
                                                                       480
ccaaatacce necacetgae nectaaccen caccateceg geaageenan ggneatttan
                                                                       540
ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana
                                                                       600
                                                                       660
aatnotootn naatttactn noantnooat caanoocacn tgaaacnnaa cocotgtttt
                                                                       720
tanatccctt ctttcgaaaa ccnacccttt annncccaac ctttngggcc ccccnctnc
                                                                       780
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
canatectat ecettanttn ggggneeett neeengggee ee
                                                                       822
      <210> 30
      <211> 787
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (787)
      <223> n = A, T, C or G
      <400> 30
eggeegeetg etetggeaca tgeeteetga atggeateaa aagtgatgga etgeecattg
                                                                        60
ctagagaaga cettetete taetgteatt atggageet geagactgag ggeteeeett
                                                                       120
gtctgcagga tttgatgtct gaagtcgtgg agtgtggctt ggagctcctc atctacatna
                                                                       180
gctggaagcc ctggagggcc tctctcgcca gcctccccct tctctccacg ctctccangg
                                                                       240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
                                                                       300
cccatqqqqc ctqnaagqcc aqqqtctcct ttqacaccat ctctcccqtc ctqcctqqca
                                                                       360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagcttttgt
                                                                       420
tecenttaat gaaggttaat tgenegettg gegtaateat nggteanaac tnttteetgt
                                                                       480
qtqaaattqt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt
                                                                       540
taaagcctgg gggtngcctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc
                                                                       600
ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca cccccnggg
                                                                       660
aaaagcggtt tgcnttttng ggggntcctt cencttecec cctenctaan ccctnegect
                                                                       720
                                                                       780
eggtegttne nggtngeggg gaangggnat nnneteeene naagggggng agnnngntat
ccccaaa
                                                                       787
      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (799)
      <223> n = A, T, C or G
      <400> 31
ttttttttt ttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac
                                                                        60
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc
                                                                       120
aacaaaggac teetgeagee ttetetgtet gtetettgge geaggeacat ggggaggeet
                                                                       180
cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
                                                                       240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                       300
```

```
ggggaccttc tgttctccca nggnaacttc ntnnatctcn aaagaacaca actgtttctt
                                                                       360
engeanttet ggetgtteat ggaaageaca ggtgteenat ttnggetggg acttggtaca
                                                                       420
tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctnttg
                                                                       480
cctgggccct taantaccca caccggaact canttantta ttcatcttng qntqqqcttq
                                                                       540
ntnateneen cetgaangeg ceaagttgaa aggeeaegee gtneeenete eecatagnan
                                                                       600
nttttnncnt canctaatgc ccccccnggc aacnatccaa tccccccccn tgggggcccc
                                                                       660
agcccangge eccegneteg ggnnneengn enegnantee ceaggntete ceantengne
                                                                       720
connngence eccgcacgca gaacanaagg ntngageene egeannnnn nggtnnenae
                                                                       780
ctcgccccc ccnncgnng
                                                                       799
      <210> 32
<211> 789
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (789)
      <223> n = A, T, C or G
60
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac
                                                                       120
ggcaacaggc teeggeggeg geggeggegg ceetacetge ggtaccaaat ntgcageete
                                                                       180
cgctcccgct tgatnttcct ctgcagctqc aggatqccnt aaaacagggc ctcggccntn
                                                                       240
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc
                                                                       300
nattaqqaat agtggtntta cccnccnccg ttggcncact ccccntggaa accacttntc
                                                                       360
gcggctccgg catctggtct taaaccttgc aaacnctggg gccctctttt tggttantnt
                                                                       420
ncongecaca atcatnacte agactggene gggetggece caaaaaanen ecceaaaace
                                                                       480
ggnccatgtc ttnncggggt tgctgcnatn tncatcacct cccgggcnca ncaggncaac
                                                                       540
ccaaaagttc ttgnggccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
                                                                       600
ccccttggcc cccaaatcct cccccgntt nctgggtttg ggaacccacg cctctnnctt
                                                                       660
tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
                                                                       720
ntectnnnca ceateceee nngnnaegne tancaangna teeettttt tanaaaeggg
                                                                       780
cccccncq
                                                                       789
      <210> 33
      <211> 793
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(793)
      <223> n = A, T, C or G
      <400> 33
gacagaacat gttggatggt ggagcacctt tctatacgac ttacaggaca gcagatgggg
                                                                        60
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg
                                                                       120
gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana
                                                                       180
agaagtttgc agatgtattt gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg
                                                                       240
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
                                                                       300
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
                                                                       360
                                                                       420
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct
                                                                       480
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac
                                                                       540
acaacatacg anccggaagc atnaaatttt aaaqcctggn ggtngcctaa tgantgaact
                                                                       600
nactcacatt aattggcttt gcgctcactg cccgctttcc agtccggaaa acctgtcctt
                                                                       660
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttgggg
                                                                       720
egenetteee getttetege tteetgaant eetteeeee ggtetttegg ettgeggena
                                                                       780
acggtatcna cct
                                                                       793
```

```
<210> 34
      <211> 756
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(756)
      <223> n = A, T, C or G
      <400> 34
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt
                                                                          60
ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg
                                                                         120
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag
                                                                         180
ateggggee aatggageat cetaegeaan gacateceet cettegageg etacatggee
                                                                         240
cageteaaat getactaett tgattacaan gageagetee eegagteage etatatgeae
                                                                         300
cagetettqq qeeteaacet cetetteetq etqteecaqa accqqqtqqe tqantnecae
                                                                         360
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca
                                                                         420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnagggtaa catccccgc cgagagctac accttcttca ttgacatcct gctcgacact atcagggatg
                                                                         480
                                                                         540
aaaatcqcnq qqttqctcca qaaaqqctnc aanaanatcc ttttcnctga aggcccccqq
                                                                         600
athenetagt netagaateg georgecate geggtggane etceaacett tegttneeet
                                                                         660
ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctgtgttga
                                                                         720
aattnttaac ccccacaat tccacgccna cattng
                                                                         756
      <210> 35
      <211> 834
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(834)
      <223> n = A, T, C or G
      <400> 35
ggggatctct anatcnacct gnatgcatgg ttgtcggtgt ggtcgctgtc gatgaanatg
                                                                          60
                                                                         120
aacaqqatct tqcccttqaa qctctcqqct qctqtnttta aqttqctcaq tctqccqtca
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat
                                                                         180
aatcttengg getgtetget eggtgaacte gatgaenang ggeagetggt tgtgtntgat
                                                                         240
aaantccanc angttctcct tggtgacctc cccttcaaag ttgttccggc cttcatcaaa
                                                                         300
                                                                         360
cttctnnaan angannance canctttgtc gagctggnat ttgganaaca cgtcactgtt
ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt
                                                                         420
                                                                         480
ggeneaaate egacteeeen teettgaaag aageenatea cacceeete eetggaetee
nncaangact ctnccgctnc ccenteenng cagggttggt ggcannccgg gcccntgcgc
                                                                         540
ttetteagee agtteaenat ntteateage ceetetgeea getgttntat teettggggg
                                                                         600
                                                                         660
ggaancegte tetecettee tgaannaact ttgacegtng gaatageege genteneent
achthetggg cegggtteaa anteceteen ttgnennten eetegggeea ttetggattt
                                                                         720
ncenaacttt tteetteece eneceenegg ngtttggntt ttteatnggg ecceaactet
                                                                         780
                                                                         834
gctnttggcc antcccctgg gggcntntan cnccccctnt ggtcccntng ggcc
      <210> 36
      <211> 814
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(814)
      <223> n = A, T, C or G
      <400> 36
```

```
cggncgcttt ccngccgcgc cccgtttcca tgacnaaggc tcccttcang ttaaatacnn
                                                                             60
 cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgccca
                                                                            120
 naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc acccctgta
                                                                            180
 ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaagtctt gtgttttact
                                                                            240
 aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg cagcctggca
                                                                            300
 ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca ggcttgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttgtc
                                                                            360
                                                                            420
 antganctgg aaggootgaa nottagtoto caaaagtoto ngoocacaag accggocaco
                                                                            480
 aggggangtc ntttncagtg gatctgccaa anantacccn tatcatcnnt gaataaaaag
                                                                            540
 gcccctgaac ganatgcttc cancancctt taagacccat aatcctngaa ccatggtgcc
                                                                            600
 cttccggtct gatccnaaag gaatgttcct gggtcccant ccctcctttg ttncttacgt
                                                                            660
 tgtnttggac centgetngn atnacecaan tganatecee ngaageacee tneeeetgge
                                                                            720
 atttganttt entaaattet etgeeetaen netgaaagea enatteeetn ggeneenaan
                                                                            780
 ggngaactca agaaggtctn ngaaaaacca cncn
                                                                            814
        <210> 37
        <211> 760
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(760)
        <223> n = A, T, C or G
        <400> 37
. gcatgctgct cttcctcaaa gttgttcttg ttgccataac aaccaccata qqtaaaqcqq
 gcgcagtgtt cgctgaaggg gttgtagtac cagcgcggga tgctctcctt qcaqaqtcct
                                                                            120
 gtgtctggca ggtccacgca atgccctttg tcactgggga aatggatgcg ctggagctcg
                                                                            180
 tenaanceae tegtgtattt tteacangea geeteeteeg aagenteegg geagttgggg gtgtegteae acteeactaa actgtegatn cancageeea ttgetgeage ggaactgggt
                                                                            240
                                                                            300
 gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat
                                                                            360
 cncctnance caaactgeet eteaaaggee acettgeaca eeeegacagg etagaaatge
                                                                            420
 actettette ecaaaggtag ttgttettgt tgeecaagea neetecanea aaceaaaane
                                                                            480
 ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn
                                                                            540
 gancencett gtttgaatge naaggnaata atecteetgt ettgettggg tggaanagea
                                                                            600
 caattgaact gttaachttg ggccgngttc chctngggtg gtctgaaact aatcaccgtc
                                                                            660
 actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctngntt tgggtnnttt
                                                                            720
 ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg
                                                                            760
       <210> 38
<211> 724
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
      · <222> (1)...(724)
       <223> n = A, T, C \text{ or } G
       <400> 38
 tttttttt tttttttt tttttttt tttttaaaaa ccccctccat tgaatgaaaa
                                                                             60
 cttccnaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc
                                                                            120
 caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa
                                                                            180
 aatttaaccc attatnaact taaatnoctn gaaacccntg gnttccaaaa atttttaacc
                                                                            240
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt
                                                                            300
 ngatttaaac ccccttnant tnttttnacc cnnqnctnaa ntatttngnt tccqqtqttt
                                                                            360
 tectnttaan entnggtaac teeegntaat gaannneet aanceaatta aacegaattt
                                                                            420
 tttttgaatt ggaaattccn ngggaattna ccggggtttt tcccntttgg gggccatncc
                                                                            480
 cccnctttcg gggtttgggn ntaggttgaa tttttnnang ncccaaaaaa ncccccaana
                                                                            540
 aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg
                                                                            600
 tttntggggg congggantt onttoccoon tinconcoo occoonggt aaanggttat
                                                                            660
```

```
720
ngnntttggt ttttgggccc cttnanggac cttccggatn gaaattaaat ccccgggncg
                                                                       724
gccg
      <210> 39
      <211> 751
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(751)
      <223> n = A, T, C or G
      <400> 39
ttttttttt ttttctttg ctcacattta atttttattt tgatttttt taatgctgca
                                                                        60
caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctgctgt
                                                                       120
tttatttatt tttactgaaa gtgagaggga acttttgtgg ccttttttcc tttttctgta
                                                                       180
ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt
                                                                       240
cqcaaaatca ctcqqqqqaa nqqaaaqqtt qctttqttaa tcatqcccta tqqtqqqtqa
                                                                       300
ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana
                                                                       360
cttgggggtt ccctcccan accaacccn ctgacaaaaa gtgccngccc tcaaatnatg
                                                                       420
teceggennt entiquaaca caengengaa ngtteteatt nteceenene cagginaaaa
                                                                       480
                                                                       540
tgaagggtta ccatntttaa cnccacctcc acntggcnnn gcctgaatcc tcnaaaancn
cocteaanen aattnetning coceggtene gentingtee eneceggget eegggaantin
                                                                       600
cacceenga annenntnne naacnaaatt eegaaaatat teeenntene teaatteeee
                                                                       660
                                                                       720
cnnaqactnt cctcnncnan cncaattttc ttttnntcac gaacncgnnc cnnaaaatgn
nnnncncctc cnctngtccn naatcnccan c
      <210> 40
      <211> 753
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (753)
      <223> n = A, T, C or G
      <400> 40
gtggtatttt ctgtaagatc aggtgttcct ccctcgtagg tttagaggaa acaccctcat
                                                                       120
agatgaaaac cccccgaga cagcagcact gcaactgcca agcagccggg gtaggagggg
                                                                       180
cgccctatgc acagctgggc ccttgagaca gcagggcttc gatgtcaggc tcgatgtcaa
                                                                       240
tgqtctqqaa qcqqcqqctq tacctqcqta qggqcacacc gtcagggccc accaggaact
teteaaagtt eeaggeaacn tegttgegae acaceggaga eeaggtgatn agettggggt
                                                                       300
                                                                       360
cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctcccgc aggaaggcna
ataaaaggtg cgccccgca ccgttcanct cgcacttctc naanaccatg angttgggct
                                                                       420
cnaacccacc accanneegg actteettga nggaatteec aaatetette gntettggge
                                                                       480
ttctnctgat gccctanctg gttgcccngn atgccaanca nccccaance ccggggtcct
                                                                       540
                                                                       600
aaancaccon cotcotontt toatotgggt tnttntcccc ggaccntggt toctotcaag
gganeceata tetenacean tacteacent necececent gnnacecane ettetanngn
                                                                       660
ttcccncccg ncctctggcc cntcaaanan gcttncacna cctgggtctg ccttccccc
                                                                       720
                                                                       753
tnccctatct gnaccccncn tttgtctcan tnt
      <210> 41
      <211> 341
      <212> DNA
      <213> Homo sapien
      <400> 41
actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaatg
                                                                        60
                                                                       120
agtgaaccca teettgattt atatacatat atgtteteag tattttggga geettteeae
tictttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt
```

```
tatagcttgt ttacgtagta agtttttqaa gtctacattc aatccagaca cttagttgag
                                                                       240
tgttaaactg tgattttaa aaaatatcat ttgagaatat tctttcagag gtattttcat
                                                                       300
ttttactttt tgattaattg tgttttatat attagggtag t
                                                                       341
      <210> 42
      <211> 101
      <212> DNA
      <213> Homo sapien
      <400> 42
acttactgaa tttagttctg tgctcttcct tatttagtgt tgtatcataa atactttgat
                                                                        60
gtttcaaaca ttctaaataa ataattttca gtggcttcat a
                                                                       101
      <210> 43
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 43
acatettigt tacagietaa gatgiqtiet taaateacea tieetteetg gieeteacee
                                                                        60
tocagggtgg totcacactg taattagage tattgaggag totttacage aaattaagat
                                                                       120
tcagatgcct tgctaagtct agagttctag agttatgttt cagaaagtct aagaaaccca
                                                                       180
cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat
                                                                       240
tggatacaga acgagagtta tcctggataa ctcagagctg agtacctgcc cgggggccgc
                                                                       300
tcgaa
                                                                       305
      <210> 44
      <211> 852
      <212> DNA
      <213> Homo sapien
      <221> misc_feature
      <222> (1) ... (852)
      <223> n = A, T, C or G
      <400> 44
acataaatat cagagaaaag tagtctttga aatatttacq tccaggagtt ctttgtttct
                                                                        60
gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt
                                                                       120
ctctccatcc togggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct
                                                                       180
ccagaatttc tcttttgtag taatatctca tagctcggct gagcttttca taggtcatgc
                                                                       240
tgctgttgtt cttctttta ccccatagct gagccactgc ctctgatttc aagaacctga
                                                                       300
agacgccctc agatcggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaga
                                                                       360
ggatgtcgcg gatgaattcc cataagtgag tecetetegg gttgtgettt ttggtgtgge
                                                                       420
acttggcagg ggggtcttgc tcctttttca tatcaggtga ctctgcaaca ggaaggtgac
                                                                       480
tggtggttgt catggagatc tgagcccggc agaaaqtttt qctgtccaac aaatctactg
                                                                       540
tgctaccata gttggtgtca tataaatagt tctngtcttt ccaggtgttc atgatggaag
                                                                       600
gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc
                                                                       660
actggccgtt ccacttcaga tgctgcaagt tgctgtagag gagntgcccc gccgtccctg
                                                                       720
ccgcccgggt gaactcctgc aaactcatgc tgcaaaggtg ctcgccgttg atgtcgaact
                                                                       780
cntggaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact
                                                                       840
cccacacctg gt
                                                                       852
      <210> 45
      <211> 234
      <212> DNA
      <213> Homo sapien
      <400> 45
acaacagacc cttgctcgct aacgacctca tgctcatcaa gttggacgaa tccgtgtccg
                                                                        60
agtotgacac catcoggage atcagcattg cttcgcagtg ccctaccgcg gggaactott
                                                                       120
gcctcgtttc tggctggggt ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg
                                                                       180
```

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tgaacqtqtc qqtqqtqtct qaqqaqqtct qcaqtaaqct ctatqacccq ctqt
                                                                         234
       <210> 46
       <211> 590
       <212> DNA
       <213> Homo sapien
      <220>
       <221> misc_feature
       <222> (1)...(590)
      <223> n = A, T, C or G
      <400> 46
actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta
                                                                           60
                                                                          120
atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa
aagaagataa tatattocaa goanatacaa aatatotaat gaaagatoaa ggoaggaaaa
                                                                          180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                          240
aaagetttea aaanaaanaa ttattgeagt etanttaatt eaaacagtgt taaatggtat
                                                                          300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                         360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                          420
                                                                         480
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
                                                                         540
qccttccttt gaggagactt catctcactg gccaacactc agtcacatgt
                                                                         590
      <210> 47
      <211> 774
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(774)
      <223> n = A,T,C or G
      <400> 47
acaagggggc ataatgaagg agtggggana gattttaaag aaggaaaaaa aacgaggccc
                                                                          60
tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                         120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                         180
                                                                         240
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                         300
cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg
                                                                         360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc
                                                                         420
ccacactect tqaacacaca tecceaggtt atatteetgg acatggetga acetectatt
                                                                         480
cctacttccq agatqccttq ctccctqcaq cctqtcaaaa tcccactcac cctccaaacc
                                                                         540
acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccctga
                                                                         600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct
                                                                         660
                                                                         720
tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                         774
      <210> 48
      <211> 124
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (124)
      <223> n = A, T, C or G
      <400> 48
canaaattqa aattttataa aaagqcattt ttctcttata tccataaaat qatataattt
                                                                          60
ttgcaantat anaaatgtgt cataaattat aatgtteett aattacaget caacgcaact
                                                                         120
```

```
tggt
                                                                       124
      <210> 49
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(147)
      <223> n = A, T, C or G
      <400> 49
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt
                                                                        60
tgtggctaca ggtggtgtct gactgcatna aaaantittt tacgggtgat tgcaaaaatt
                                                                        120
ttagggcacc catatcccaa gcantgt
                                                                       147
      <210> 50
      <211> 107
      <212> DNA
      <213> Homo sapien
acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatqqctt qatatattqc
                                                                         60
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt
                                                                       107
      <210> 51
      <211> 204
      <212> DNA
      <213> Homo sapien
gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg
                                                                        60
cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag
                                                                       120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca
                                                                       180
cctccctttt gggaccagca atgt
                                                                       204
      <210> 52
      <211> 491
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (491)
      <223> n = A, T, C or G
      <400> 52
acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaaggtta gtattgtgta
                                                                        60
gggtattttc caaaagacta aagagataac tcaqqtaaaa aqttaqaaat qtataaaaca
                                                                       120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa
                                                                       180
aaaacttett gtatcaattt ettttgttea aaatgaetga ettaantatt tttaaatatt
                                                                       240
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcagtccca
                                                                       300
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc
                                                                       360
atgcaacagt gtctttctt tnctttttct ttttttttt ttacaggcac agaaactcat
                                                                       420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat
                                                                       480
atcactcttg t
                                                                       491
      <210> 53
      <211> 484
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc_feature
      <222> (1) ... (484)
      <223> n = A, T, C or G
      <400> 53
acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga
                                                                        60
                                                                       120
gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct
                                                                       180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct
                                                                       240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                       300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                       360
aatgattgqc aggtenggta aatnecaaaa catattecaa etcaacaett etttteeneg
                                                                        420
                                                                       480
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc
                                                                        484
cant
      <210> 54
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 54
                                                                        60
actaaacctc qtqcttqtqa actccataca qaaaacqqtq ccatccctga acacqgctgg
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag
                                                                       120
tctatgtcct ctcaagtgcc tttttgtttg t
                                                                       151
      <210> 55
      <211> 91
      <212> DNA
      <213> Homo sapien
      <400> 55
acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc
                                                                        60
gccctccagt ggatactcga gccaaagtgg t
                                                                        91
      <210> 56
      <211> 133
      <212> DNA
      <213> Homo sapien
      <400> 56
ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact
                                                                        60
tgqatttttq gtatctqtqq gttgggggga cggtccagga accaataccc catggatacc
                                                                       120
                                                                       133
aagggacaac tgt
      <210> 57
      <211> 147
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1) ... (147)
     <223> n = A, T, C or G
      <400> 57
actotggaga acctgageeg etgeteegee tetgggatga ggtgatgean gengtggege
                                                                        60
gactgggage tgagecette cetttgegee tgeeteagag gattgttgee gaentgeana
                                                                       120
                                                                       147
tctcantggg ctggatncat gcagggt
```

<210> 58

```
<211> 198
        <212> DNA
        <213> Homo sapien
       <220>
       <221> misc_feature
        <222> (1) ... (198)
       <223> n = A, T, C or G
       <400> 58
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc
                                                                          60
 tgattacata catttatcci ttaaaaaaga tgtaaatctt aatttttatg ccatctatta
                                                                         120
 atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt
                                                                         180
 ttgacttcta agtttggt
                                                                         198
       <210> 59
       <211> 330
       <212> DNA
       <213> Homo sapien
 acaacaaatg ggttgtgagg aagtcttatc agcaaaactg gtgatqqcta ctqaaaaqat
                                                                          60
 ccattgaaaa ttatcattaa tgattttaaa tgacaagtta tcaaaaaactc actcaatttt
                                                                         120
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa
                                                                         180
 tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagacccag
                                                                         240
 cagaaggaat ctatttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt
                                                                         300
. tttcgtcttt attggacttc tttgaagagt
                                                                         330
       <210> 60
       <211> 175
       <212> DNA
       <213> Homo sapien
       <400> 60
 accgtgggtg ccttctacat tcctgacggc tccttcacca acatctggtt ctacttcggc
                                                                         60
 gtcgtgggct ccttcctctt catcctcatc cagctggtgc tgctcatcga ctttgcgcac
                                                                        120
 tcctggaacc agcggtggct gggcaaggcc gaggagtgcg attcccgtgc ctggt
                                                                        175
       <210> 61
       <211> 154
       <212> DNA
       <213> Homo sapien
       <400> 61
 accocacttt teeteetgtg ageagtetgg actteteact getacatgat gagggtgagt
                                                                         60
 ggttgttgct cttcaacagt atcctccct ttccggatct gctgagccgg acagcagtgc
                                                                        120
 tggactgcac agccccgggg ctccacattg ctgt
                                                                        154
       <210> 62
       <211> 30
       <212> DNA
       <213> Homo sapien
       <400> 62
 cgctcgagcc ctatagtgag tcgtattaga
                                                                         30
       <210> 63
       <211> 89
       <212> DNA
       <213> Homo sapien
       <400> 63
```

```
acaagtcatt tcaqcaccct ttqctcttca aaactgacca tcttttatat ttaatqcttc
                                                                         60
ctgtatgaat aaaaatqqtt atqtcaaqt
                                                                         89
      <210> 64
      <211> 97
      <212> DNA
      <213> Homo sapien
      <400> 64
accggagtaa ctgaqtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcaq
                                                                         60
aatcagtgca tccaggattg gtccttggat ctggggt
                                                                         97
      <210> 65
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (377)
      <223> n = A,T,C or G
      <400> 65
acaacaanaa ntoocttott taggocactg atggaaacct ggaaccccct tttgatggca
                                                                         60
gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntcccaa accgcacacc
                                                                       120
ccaaccctgg tctacccaca nttctggcta tgggctgtct ctgccactga acatcagggt
                                                                       180
tcggtcataa natqaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa
                                                                       240
ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg
                                                                       300
tgggggtgaa ctacccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag
                                                                        360
gggcgggagg agcatgt
                                                                       377
      <210> 66
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 66
acgcctttcc ctcagaattc agggaagaga ctgtcgcctg ccttcctccg ttgttgcgtg
                                                                        60
agaaccegtg tgccccttcc caccatatcc accetegete catctttgaa ctcaaacacg
                                                                       120
aggaactaac tgcaccctgg tecteteece agtececagt teacceteea teceteacet
                                                                       180
tectecacte taagggatat caacactgee cageacaggg geeetgaatt tatgtggttt
                                                                       240
ttatatattt tttaataaga tgcactttat gtcattttt aataaagtct gaagaattac
                                                                       300
                                                                       305
tattt
      <210> 67
      <211> 385
      <212> DNA
      <213> Homo sapien
      <400> 67
actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga
                                                                        60
ggtcggacca gccacatctc atgtgcaaga ttgcccagca gacatcaggt ctgagagttc
                                                                       120
cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc
                                                                       180
tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg
                                                                       240
ctgggcaqtc ttgcacatga gatggggctq gtctgatctc agcactcctt aqtctgcttg
                                                                       300
cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac
                                                                       360
catagtttct gtgctagtgg accgt
                                                                       385
     <210> 68
     <211> 73
      <212> DNA
     <213> Homo sapien
```

```
<400> 68
acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                         60
gtttttttaa tgg
                                                                        73
      <210> 69
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (536)
      <223> n = A, T, C or G
      <400> 69
actagtccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcagc
                                                                        60
tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct
                                                                       120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat
                                                                       180
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt
                                                                       240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                       300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                       360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc
                                                                       420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                       480
gaanqtccct gggtgaaatc caggtgtcaa qaaatcctan ggatctgttg ccaggc
                                                                       536
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 70
atgaccecta acaggggeee teteageeet cetaatgace teeggeetag ceatgtgatt
                                                                        60
tcacttccac tccataacqc tcctcatact aggcctacta accaacacac taaccatata
                                                                       120
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt
                                                                       180
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc
                                                                       240
agggattttt ctgagccttt taccactcca gcctagcccc taccccccaa ctaggagggc
                                                                       300
actggcccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
                                                                       360
ccgtattact cgcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca
                                                                       420
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt
                                                                       477
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (533)
      <223> n = A,T,C or G
      <400> 71
agagetatag gtacagtgtg ateteagett tgcaaacaca ttttetacat agatagtact
                                                                        60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
                                                                       120
tgtqatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                       180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt
                                                                       240
taaataaagg tttgtcatct ttaaaaaatac agcaatatgt gacttttaa aaaagctgtc
                                                                       300
aaataggtgt gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca
                                                                       360
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                       420
cttcgtaatt ttggagtang aggttccctc ctcaattttg tatttttaaa aagtacatgg
                                                                       480
taaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                       533
```

```
<211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 72
tattacqqaa aaacacaca cataattcaa ctancaaaqa anactqcttc aqqqcqtqta
                                                                      60
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
                                                                     120
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga
                                                                     180
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt
                                                                     240
gaggttetet gtgtgeecae tggtttgaaa accgttetne aataatgata gaatagtaca
                                                                     300
cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcagaanac
                                                                     360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg
                                                                     420
atttetete attgeagena naaaceegtt ettetaagea aacneaggtg atgatggena
                                                                     480
aaatacaccc cctcttgaag naccnggagg a
                                                                     511
      <210> 73
      <211> 499
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (499)
      <223> n = A, T, C or G
     <400> 73
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac
                                                                      60
                                                                     120
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta
                                                                     180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                     240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
                                                                     300
360
antitaqaqq gecegtttaa accegetgat cageetegae tgtgeettet anttgecage
                                                                     420
catctqttqt ttqcccctcc cccqntqcct tccttqaccc tqqaaaqtqc cactcccact
                                                                     480
gtcctttcct aantaaaat
      <210> 74
      <211> 537
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(537)
      <223> n = A, T, C or G
      <400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
                                                                      60
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
                                                                     120
tccaggcca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                     180
                                                                     240
cattqtatqc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
aaaqaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag
                                                                     300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                     360
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
                                                                     420
actgaaaaan qaatgatata ttcttgaaga catcgatata catttattta cactcttgat
                                                                     480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt
                                                                     537
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<210> 75
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (467)
      <223> n = A, T, C or G
      <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
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tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca
                                                                          120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                          180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
                                                                          240
totagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                          300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                          360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                          420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
                                                                          467
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(400)
      <223> n = A, T, C or G
      <400> 76
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctcgcgctac
                                                                           60
tetetette tggcetggag getatecage gtactecaaa qatteaggtt tacteacgte
                                                                          120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat
                                                                          180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag acttgtcttt cagcaaggac tggtctttct atctcttgta ctacactgaa ttcaccccca
                                                                          240
                                                                          300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                          360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                          400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
      <400> 77
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                           60
ccagetgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgctgc
                                                                          120
caggiactit toatotoago tittotito cittigotoco giocaagogot totigotigaaa
                                                                          180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                          240
aaaaaaa
                                                                          248
      <210> 78
      <211> 201
      <212> DNA
      <213> Homo sapien
      <400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                           60
teacecagae ecegeeetge eegtgeeeca egetgetget aacgacagta tgatgettae
                                                                          120
tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttgttt ataaatgcct
                                                                          180
gatttaaaaa aaaaaaaaa a
                                                                          201
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<210> 79
       <211> 552
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(552)
       <223> n = A, T, C or G
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tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt
                                                                          120
cctctttctt ctgaagatta atgaagttga aaattqaggt qqataaatac aaaaaggtag
                                                                          180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                          240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact
                                                                          300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta
                                                                          360
                                                                          420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                          480
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                          540
aaaaaaaaa aa
                                                                          552
       <210> 80
      <211> 476
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (476)
      <223> n = A, T, C or G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
                                                                           60
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct
                                                                          120
cacacagact cocgagtage tgggactaca ggcacacagt cactgaagca ggccctgttt
                                                                          180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta
                                                                          240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                          300
tettetaagt cetetteeag ceteactitg agteeteett gggggttgat aggaaninte
                                                                          360
tettggettt etcaataaaa tetetateea teteatgttt aatttggtae gentaaaaat
                                                                          420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaa aaaaaa
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(232)
      <223> n = A, T, C or G
      <400> 81
tttttttttg tatgccntcn ctgtggngtt attgttgctg ccaccctgga ggagcccagt
                                                                           60
ttettetgta tetttetttt etgggggate tteetggete tgeeceteca tteecageet
                                                                          120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                          180
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct
                                                                          232 \
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
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<220>
        <221> misc_feature
        <222> (1)...(383)
        <223> n = A,T,C or G
        <400> 82
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                                                                             60
 agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg
                                                                            120
 gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                            180
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt
                                                                            240
 gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac
                                                                            300
 agcactctng gcagccacta tcaatcaatt gaaqttgaca ctctgcatta aatctatttg
                                                                            360
 ccatttcaaa aaaaaaaaaa aaa
                                                                            383
        <210> 83
        <211> 494
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(494)
        <223> n = A, T, C or G
        <400> 83
. accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
                                                                             60
 gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc
                                                                           120
 ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa
                                                                           180
 acgetteaag gtgeteatga cecageaace gegeeetgte etetgagggt cettaaactg
                                                                           240
 atgtetttte tgccacetgt taccectegg agacteegta accaaactet teggactgtg
                                                                           300
 agocctgatg cotttttgcc agocatactc tittggcntcc agtototogt ggcgattgat
                                                                           360
 tatgcttqtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttgantttt
                                                                           420
 tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta
                                                                           480
 aaaaaaaaa aaaa
                                                                           494
       <210> 84
       <211> 380
        <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(380)
       <223> n = A, T, C or G
       <400> 84
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                                                                            60
                                                                           120
 gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                           180
 gcacaccete etggggecca ggegggeace tgegtetece agtatgceaa etggetggtg
                                                                           240
 gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
                                                                           300
 ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc
                                                                           360
 agcqttnccq cctcatccgg
                                                                           380
       <210> 85
       <211> 481
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
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<222> (1)...(481)
       <223> n = A, T, C or G
       <400> 85
gagttagete etecacace ttgatgaggt egtetgeagt ggeetetege tteatacege
tnecategte atactgtagg tttgccacca cetectgcat ettggggegg etaatateca
                                                                             120
ggaaactetc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg
                                                                             180
tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga
                                                                             240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagtgag gtcaccagcc
                                                                             300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac
                                                                            360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
                                                                             420
aaagaacacc tootggaagt gotngooget cotogtoont tggtggnngo gontnoottt
                                                                            480
                                                                             481
      <210> 86
      <211> 472
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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       <223> n = A,T,C or G
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acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt
                                                                            120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg
                                                                            180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt
                                                                            240
                                                                            300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg
                                                                            360
atatntgage ggaagantag cetttetact teaceagaca caacteettt catattggga
                                                                            420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                            472
      <210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (413)
      <223> n = A, T, C or G
      <400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg tgtgtgtgcg cgcatattat atagacaggc acatctttt tacttttgta aaagcttatg
                                                                             60
                                                                            120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                            180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                            240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg
                                                                            300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
                                                                            360
acagaaattg ggtngtatat tgaaananng catcattnaa acgtttttt ttt
                                                                            413
      <210> 88
      <211> 448
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(448)
      <223> n = A, T, C or G
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cgcagcgggt cotototate tagetecage etetegeetg ceccaetece egegtecege
                                                                        60
gteetageen accatggeeg ggeeeetgeg egeeegetg eteetgetgg eeateetgge
                                                                       120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                       180
gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttgccg
                                                                       240
teggenanta caacaaacce geaacnactt ttacenagen egegetgeag gttgtgeege
                                                                       300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng
                                                                       360
tttaccagaa ccnagccaat tngaacaatt nccctccat aacagcccct tttaaaaagg
                                                                       420
gaancantcc tgntcttttc caaatttt
                                                                       448
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (463)
      <223> n = A, T, C or G
      <400> 89
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                                                                        60
qtaqtqattc tqccaaaqtt qqtqttqtaa catqaqtatq taaaatqtca aaaaattaqc
                                                                       120
agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt
                                                                       180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc
                                                                       240
tttnatgttn agacttgcct ctntnaaatt qcttttgtnt tctqcaqqta ctatctqtqq
                                                                       300
tttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn
                                                                       360
aattetete ccatannaaa acceangee ttggganaat ttgaaaaang gnteettenn
                                                                       420
aattennana antteagntn teatacaaca naaenggane eec
                                                                       463
      <210> 90
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (400)
      <223> n = A, T, C or G
      <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
cttccactca ctqtctqtaa qcntnttaac ccaqactqta tcttcataaa taqaacaaat
                                                                       120
tetteaceag teacatette taggacettt ttggatteag ttagtataag etetteeact
                                                                       180
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattgct
                                                                       240
cgttctctaa caatqtcctc tccttqaaqt atttqqctqa acaacccacc tnaaqtccct
                                                                       300
ttgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctgcaa
                                                                       360
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
                                                                       400
      <210> 91
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      <223> n = A, T, C or G
      <400> 91
gageteggat ecaataatet ttgtetgagg geageacaea tatneagtge eatggnaact
                                                                        60
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31

120

180

240

ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac

atgeetettt gaetaeegtg tgeeagtget ggtgattete acacacetee nneegetett

tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga

gacacttgaa aqqtqtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt 300 tgtcaatact aacccgctgg tttgcctcca tcacatttgt gatctgtagc tctggataca 360 tctcctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctgtt 420 ngatcaggtt cccatttccc agtccgaatg ttcacatggc atainttact tcccacaaaa 480 <210> 92 <211> 477 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1) ... (477) <223> n = A, T, C or G<400> 92 atacagecca nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteaet 60 ggtcccgctg tagccccagc gactetccac ctgctggaag cggttgatgc tgcactcctt 120 cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt 180 240 taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca 300 gaacetteeg eetgttetet ggegteacet geagetgetg eegetnacae teggeetegg accageggae aaacggegtt gaacageege accteacgga tgeecantgt gtegegetee 360 420 aggaacggen ccagcgtgtc caggtcaatg teggtgaanc eteegegggt aatggeg 477 <210> 93 <211> 377 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1) ... (377) <223> n = A, T, C or G<400> 93 qaacqqctqq accttqcctc gcattqtqct qctqqcaqqa ataccttqqc aaqcaqctcc 120 agtocgagea geoceagace getgeegeee gaagetaage etgeetetgg cetteecete cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn 180 tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa 240 caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta 300 aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa 360 ataaatatat tattaaa 377 <210> 94 <211> 495 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (495) <223> n = A, T, C or G<400> 94 ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc 60 cgagctgang cagatttccc acagtgaccc cagagccctg ggctatagtc tctgaccct 120 ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg 180 gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgccccc 240

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acgaggaana ggccctgant cctgggatca nacaccctt cacgtgtatc cccacacaaa
                                                                        300
tgcaagetea ccaaggteee eteteagtee etteeetaca ecetgaacqq neactggeee
                                                                        360
acacccaccc agancancca cccgccatgg ggaatgtnct caaggaatcg engggcaacg
                                                                        420
tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana
                                                                        480
aaaaaaaana aaaaa
                                                                        495
      <210> 95
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (472)
      <223> n = A,T,C or G
      <400> 95
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                         60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                        120
tagetgtttt gagttgatte geaceactge accaeaacte aatatgaaaa etatttnact
                                                                        180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt
                                                                        240
atgatgaaaa gcaatagata tatattottt tattatgttn aattatgatt gccattatta
                                                                        300
atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac
                                                                        360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata
                                                                        420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at
                                                                        472
      <210> 96
      <211> 476
      <212> DNA
      <213> Homo sapien
      <221> misc_feature
      <222> (1) ... (476)
      <223> n = A, T, C or G
      <400> 96
ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat
                                                                         60
gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaaqtctt
                                                                        120
ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt
                                                                        180
attetteaca gtagatgatg aaagagteet eeagtgtett gngcanaatg ttetagntat
                                                                        240
agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat
                                                                        300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct
                                                                        360
gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt
                                                                        420
tacaaagtct atcttcctca nangtctgtn aaggaacaat ttaatcttct agcttt
                                                                        476
      <210> 97
     · <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (479)
      <223> n = A, T, C or G
      <400> 97
actctttcta atgctgatat gatcttgagt ataagaatgc atatgtcact agaatggata
                                                                        60
aaataatgct gcaaacttaa tgttcttatg caaaatggaa cgctaatgaa acacagctta
                                                                       120
caatcgcaaa tcaaaactca caagtgctca tctgttgtag atttagtgta ataagactta
                                                                       180
gattgtgctc cttcggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat
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Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly
                    215
                                    220
Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His
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Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu 245 250 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg 260 265 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe 280 285 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val 295 300 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly 310 315 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu 330 325 335 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg 340 345 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala 355 360 365 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu 375 380 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala 390 395 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly 405 410 415 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu 420 425 430 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala 435 . 440 Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser 450 455 460 Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala 470 475 - 480 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp 485 490 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser 500 505 510 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala 520 525 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp 535 540 Lys Ser Asp Leu Ala Lys Tyr Ser Ala 550 545

<210> 114

<211> 241

<212> PRT

<213> Homo sapien

<400> 114

Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu 10 Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val 20 Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser 40 45 Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly 55 Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile 90 85 Phe Ile Ala Glu Val Ala Ala Ala Val Ala Leu Val Tyr Thr Thr 105 100 110 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys

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115
                             120
                                                 125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
    130
                       135
                                             140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
                     150
                                         155
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                                                         175
                                     170
                165
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
            180
                                 185
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
                             200
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
                         215
                                             220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
225
                     230
                                         235
Gln
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      <211> 366
      <212> DNA
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getetttete teeceteete tgaatttaat tettteaact tgeaatttge aaggattaca
                                                                         60
catttcactg tgatgtatat tgtgttgcaa aaaaaaaaa gtgtctttgt ttaaaattac
                                                                        120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                        180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                        240
tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaat tagtttgggt
                                                                        300
tetetacatg cataacaaac eetgetecaa tetgteacat aaaagtetgt gaettgaagt
                                                                        360
ttagtc
                                                                        366
      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien
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      <221> misc_feature
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      <223> n = A, T, C or G
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acaaaqatqa accatttcct atattataqc aaaattaaaa tctacccqta ttctaatatt
                                                                         60
                                                                        120
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
                                                                        180
atacqttaaa caaaqqataa tqtqaacaqc agaqaqqatt tqttqqcaqa aaatctatqt
                                                                        240
tcaatctnga actatctana tcacagacat ttctattcct tt
                                                                        282
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      <211> 305
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A, T, C or G
      <400> 117
acacatgtcg cttcactgcc ttcttagatg cttctggtca acatanagga acagggacca
                                                                         60
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa
                                                                        120
```

```
aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                        180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt
                                                                        240
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
                                                                        300
tgggt
                                                                        305
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      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A, T, C or G
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                                                                         60
aantcctggg t
                                                                         71
      <210> 119
      <211> 212
      <212> DNA
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      <220>
      <221> misc feature
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      <223> n = A, T, C or G
      <400> 119
actocggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca
                                                                         60
gaaaatqqqq tqaaattqqc caactttcta tnaacttatq ttqqcaantt tqccaccaac
                                                                        120
                                                                        180
agtaagctgg cccttctaat aaaagaaaat tgaaaggttt ctcactaanc ggaattaant
aatggantca aganactccc aggcctcagc gt
                                                                        212
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      <211> 90
      <212> DNA
      <213> Homo sapien
      <220>
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      <223> n = A, T, C or G
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actogttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggtcttgcc
                                                                         60
ctccgccggc gcagaacatg ctggggtggt
                                                                         90
      <210> 121
      <211> 218
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (218)
      <223> n = A, T, C or G
      <400> 121
tgtancgtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga
                                                                         60
gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag
                                                                        120
```

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atatncangt agcatanact	aaattangga tcatgtgggg	atgaattcat atancagcta	ggttcttttg cccttgta	ggaattcctt	tacgatngcc	180 218
<211 <212	> 122 > 171 > DNA > Homo sapi	en				
	> 122	aggacaaaaa	ttgagactca	actoocttaa	ccaataaagg	60
catttgttag	ctcatggaac	aggaagtcgg ctgtgccaca	atggtggggc	atcttcagtg	ctgcatgagt	120 171
<211 <212	> 123 > 76 > DNA > Homo sapi	en				
<220						
<222	> misc_feats > (1)(76 > n = A,T,C	)				-
	> 123	>+ aa+ a+ a+ a	ctatactata	02002202	+++>++>	60
ttatcaanta		atggtgtgtg	ctgtgttate	caggaacaca	CCCaccacca	76
	> 124 > 131					
	> DNA > Homo sapie	en			•••	
	> 124					
	ggtcatatgg	tcctgtgtgc aggggaggag				60 120 131
<210 <211						
<212	> DNA > Homo sapie	en				
<4000		aatagatggt	ggaaaattgc	gttaccaact	ataccactoo	60
cttgaaaaag	aggtgatagc	tcttcagagg aaatgaagat	acttgtgact	tttgctcaga	tgctgaagaa	120 180
ttgcctcacc	aaacaaaagt	gaaacaactg tttgagaatg	agagaaaatt	ttcaggaaaa	aagacagtgg	240 300
	cagaaccact	tgtaagaatg attttctagc				360 420 432
<210 <211						
<212> <213>	→ DNA → Homo sapie	en				
<400>		tagaaactga	actaaaattt	ctaattcact	ttotaaccat	60
		ccagggatca				112

<210> 127

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<211> 54
       <212> DNA
       <213> Homo sapien
       <400> 127
accacgaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag
                                                                            54
       <210> 128
      <211> 323
       <212> DNA
       <213> Homo sapien
       <400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc
                                                                            60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttqc tctctqctca
                                                                           120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttccttt tcttagcctt
                                                                           180
                                                                           240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct
                                                                           300
aggetgeett etttteeatg tee
                                                                           323
      <210> 129
      <211> 192
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (192)
      <223> n = A,T,C or G
      <400> 129
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatac
                                                                            60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc
                                                                           120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
                                                                           180
gataaacaaa gt
                                                                           192
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      <211> 362
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (362)
      <223> n = A, T, C \text{ or } G
      <400> 130
cccttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca
                                                                            60
tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa
                                                                           120
gtttccattg tgttttgccg atcttctggc taatcqtqqt atcctccatq ttattaqtaa
                                                                           180
ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata
                                                                           240
cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat
                                                                           300
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt qctaatctta aaaagtaatg
                                                                           360
gg
                                                                           362
      <210> 131
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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<222> (1)...(332)
      <223> n = A, T, C or G
ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca.
                                                                         60
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga
                                                                        120
gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc
                                                                        180
ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa
                                                                        240
cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc
                                                                        300
atanaaggat tgggtgaagc tggcgttgtg gt
                                                                        332
      <210> 132
      <211> 322
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (322)
      <223> n = A, T, C \text{ or } G
      <400> 132
                                                                         60
acttttqcca ttttqtatat ataaacaatc ttgggacatt ctcctgaaaa ctaggtqtcc
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat
                                                                        120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
                                                                        180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg
                                                                        240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
                                                                        300
gtaacaatct acaattggtc ca
                                                                        322
      <210> 133
      <211> 278
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (278)
      <223> n = A, T, C \text{ or } G
acaagcette acaagtttaa etaaattggg attaatettt etgtanttat etgeataatt
                                                                         60
cttgttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
                                                                        120
ctatttaaaa aaaatcacaa atctttccct ttaaqctatq ttnaattcaa actattcctq
                                                                        180
                                                                        240
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
                                                                        278
cccacgaaac actaataaaa accacagaga ccagcctg
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(121)
      <223> n = A, T, C or G
      <400> 134
qtttanaaaa cttqtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                         60
tgattctctq aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg
                                                                        120
                                                                        121
```

<210> 135

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<211> 350
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A,T,C or G
      <400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
                                                                         60
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc
                                                                        120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtactcca
                                                                        180
gggtgcccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct
                                                                        240
ccacctcaat caagccctgg gccatgctac ctgcaattgg ctgaacaaac gtttgctgag
                                                                        300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt
                                                                        350
      <210> 136
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (399)
      <223> n = A, T, C or G
      <400> 136
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt
                                                                        60
gctgtgattg tatccgaata ntcctcgtga qaaaagataa tgagatqacq tgagcagcct
                                                                        120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                        180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag
                                                                        240
aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                        300
toccaggaac cogggcaaag gccatoccca cotacagcca gcatgcccac tggcgtgatg
                                                                        360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt
                                                                        399
      <210> 137
      <211> 165
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A, T, C or G
actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt
                                                                        60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga
                                                                       120
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
                                                                       165
      <210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (338)
      <223> n = A, T, C or G
      <400> 138
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                                                                            60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                           120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                           180
                                                                           240
cangceteag gaageeteaa gtteeattea getttgeeae tgtacattee eeatntttaa
                                                                           300
aaaaactgat gcctttttt tttttttttt taaaattc
                                                                           338
      <210> 139
      <211> 382
      <212> DNA
     <213> Homo sapien
      <400> 139
gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa
                                                                            60
gaaagggact togagtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga
                                                                           120
atteaaacag acctegteat teetggtgtg ageetggteg geteacegee tateatetge
                                                                           180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg
                                                                           240
cettatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat
                                                                           300
qtcaqctatq tqccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagtg
                                                                           360
gcctggaact tgtttaaagt gt
                                                                           382
      <210> 140
<211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(200)
      <223> n = A, T, C or G
      <400> 140
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                            60
actiticati taacanctit tgttaagtgt caggetgeae titgeteeat anaattatig
                                                                           120
                                                                           180
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                           200
atattcagca taaaggagaa
      <210> 141
      <211> 335
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (335)
      <223> n = A, T, C or G
      <400> 141
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg
                                                                           60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt
                                                                          120
                                                                          180
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga
                                                                          240
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg
                                                                          300
attcacaaac caagtaattt taaacaaaga cactt
                                                                          335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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<222> (1)...(459)
      <223> n = A, T, C or G
      <400> 142
accaggttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta
                                                                            60
gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat
                                                                           120
ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca
                                                                           180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc
                                                                           240
ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga
                                                                           300
                                                                           360
agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct
                                                                           420
cagcangggt gggaggaacc agctcaacct tggcgtant
                                                                           459
      <210> 143
      <211> 140
      <212> DNA
      <213> Homo sapien
      <400> 143
acatttcctt ccaccaagtc aggactcctg gcttctgtgg gagttcttat cacctgaggg
                                                                           60
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag
                                                                           120
accatccgac ttccctqtqt
                                                                           140
      <210> 144
      <211> 164
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(164)
      <223> n = A, T, C or G
      <400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct
                                                                           60
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg
                                                                           120
aggcaattaa tocatatttg ttttcaataa ggaaaaaaaag atgt
                                                                           164
      <210> 145
      <211> 303
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(303)
      <223> n = A, T, C or G
      <400> 145
acgtagacca tocaactttg tatttgtaat ggcaaacatc cagnagcaat toctaaacaa
                                                                           60
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat
                                                                           120
gcaggacage tatcataagt cggcccagge atccagatac taccatttgt ataaacttca
                                                                          180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag
                                                                          240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccqtqq tgattaccat
                                                                          300
                                                                          303
caa
      <210> 146
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
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<221> misc feature
      <222> (1) ... (327)
      <223> n = A, T, C or G
      <400> 146
actgcaqctc aattaqaaqt qqtctctqac tttcatcanc ttctccctqq gctccatgac
                                                                       120
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                       180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                       240
agacttqccc ctqqqcctgt cacacctact gatqaccttc tgtqcctgca ggatggaatq
                                                                       300
                                                                       327
taggggtgag ctgtgtgact ctatggt
      <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (173)
      <223> n = A, T, C or G
      <400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg
                                                                        60
actggaacac atacccacat ctttqttctg agggataatt ttctgataaa gtcttgctqt
                                                                       120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                       173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(477)
      <223> n = A, T, C or G
      <400> 148
acaaccactt tatctcatcq aatttttaac ccaaactcac tcactgtgcc tttctatcct
                                                                        60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact
                                                                       120
gecetactae etgetgeaat aateacatte cetteetgte etgaceetga agecattggg
                                                                       180
qtqqtcctaq tqqccatcag tccangcctg caccttgagc ccttgagctc cattgctcac
                                                                       240
necaneceae etcacegace ecatectett acacagetae etcettgete tetaacecea
                                                                       300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
                                                                       360
caccactggt aagcettete cagecaacac acacacacac acacneacac acacacatat
                                                                       420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg
                                                                       477
      <210> 149
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 149
acaqttqtat tataatatca agaaataaac ttgcaatgaq agcatttaaq agggaaqaac
                                                                        60
taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                       120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                       180
tttcaggcag agggaacagc agtgaaa
                                                                       207
      <210> 150
      <211> 111
      <212> DNA -
      <213> Homo sapien
```

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<220>
      <221> misc_feature
      <222> (1) ... (111)
      <223> n = A, T, C or G
      <400> 150
accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg
                                                                        60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t
                                                                       111
      <210> 151
      <211> 196
      <212> DNA
      <213> Homo sapien
      <400> 151
agcgcggcag gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac
                                                                        60
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat
                                                                       120
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacqag
                                                                       180
                                                                       196
gtgcatccgg ctcagt
      <210> 152
      <211> 132
      <212> DNA
      <213> Homo sapien
      <400> 152
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac
                                                                       60
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga atagaaccag
                                                                       120
gagggagttt gt
                                                                       132
      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (285)
      <223> n = A, T, C or G
      <400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag
cttctqctct tatqtcctca tctqacaact ctttaccatt tttatcctcq ctcaqcaqqa
                                                                       120
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatcaacac
                                                                       180
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca
                                                                       240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt.
                                                                       285
      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien
      <400> 154
accacagtcc tgttgggcca gggcttcatg accctttctg tgaaaagcca tattatcacc
                                                                        60,
accccaaatt tttccttaaa tatctttaac tgaaqqqqtc aqcctcttqa ctgcaaaqac
                                                                       120
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg
                                                                       180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg
                                                                       240
agtiticacaa atteteggge cacetegtea tigeteetet gaaataaaat eeggagaatg
                                                                       300
gtcaggcctg tctcatccat atggatcttc cgg
                                                                       333
```

<210> 155

```
<211> 308
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (308)
      <223> n = A, T, C or G
      <400> 155
actqqaaata ataaaaccca catcacagtq ttgtgtcaaa gatcatcagg gcatggatgg
                                                                         60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                        120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag ccccagcccc
                                                                        180
                                                                        240
atcacaqctc actqctctqt tcatccaggc ccagcatgta gtggctgatt cttcttggct
qcttttaqcc tccanaaqtt tctctgaagc caaccaaacc tctangtgta aggcatgctg
                                                                        300
                                                                        308
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta
                                                                         60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                        120
qaataqqaqa ttatqtttqq ccctcatatt ctctcctatc ctccttgcct cattctatgt
                                                                        180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                        240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat
                                                                        295
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
                                                                        60
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
qaaqaqcaaa acaaattciq tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc
                                                                        120
                                                                        126
cttagt
      <210> 158
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(442)
      <223> n = A, T, C or G
      <400> 158
                                                                        60
acceactqqt cttqgaaaca cccatcctta atacgatgat ttttctqtcq tqtgaaaatq
                                                                        120
aanccaqcaq qctqccccta qtcaqtcctt ccttccaqaq aaaaaqaqat ttgaqaaagt
                                                                        180
qcctqqqtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta
                                                                        240
                                                                        300
natqtttqta qccttqcata cttaqccctt cccacqcaca aacqqaqtqg caqaqtqgtg
                                                                        360
ccaaccetgt tttcccagte cacgtagaca gattcacagt geggaattet ggaagetgga
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg
                                                                        420
tgttcattct ctgatgtcct gt
                                                                        442
      <210> 159
```

<211> 498

<212> DNA

```
<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(498)
      <223> n = A, T, C or G
      <400> 159
acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc
                                                                        60
tccaacaaga actgaggttg cagagcgggt agggaagagt gctgttccag ttgcacctgg
                                                                       120
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag
                                                                       180
gtgtgttgtt gganttgagc tcgggcggct gtggtaggtt gtgggctctt caacaggggc
                                                                       240
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaaqt
                                                                       300
antanattet teetgaagge eagegettgt ggagetggea ngggteantg ttgtgtgtaa
                                                                       360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn
                                                                       420
tcaggtaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc
                                                                       480
aagggaataa gctgtggt
                                                                       498
      <210> 160
      <211> 380
      <212> DNA
    < <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (380)
      <223> n = A, T, C or G
      <400> 160
acctgcatcc agcttccctg ccaaactcac aaggagacat caacctctag acagggaaac
                                                                        60
agetteagga taetteeagg agacagagee accageagea aaacaaatat teecatgeet
                                                                       120
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc
                                                                       180
cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc
                                                                       240
ccaccettae etecatetea cacacttgag etttecaete tgtataatte taacateetg
                                                                       300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa
                                                                       360
cttqtaqaat qaaqcctqqa
                                                                       380
      <210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
actocacate coetetgage aggeggttgt egtteaaggt gtatttggee ttgcetqtea
                                                                        60
cactificate tiggecenta tocactified gettaateen togaaagage atgt
                                                                       114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
actttctgaa tcgaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa
                                                                        60
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
                                                                       120
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                       177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
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```
<221> misc_feature
      <222> (1) ... (137)
      <223> n = A, T, C or G
      <400> 163
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccqtgac
                                                                         60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctqcacctt
                                                                        120
catcagcggc atgatgt
                                                                        137
      <210> 164
      <211> 469
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (469)
      <223> n = A, T, C or G
      <400> 164
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta
                                                                         60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                        120
tgcatggatc tcaaaggaaa caaacacca ataaactcgg agtggcagac tgacaactgt
                                                                        180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg
                                                                        240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                        300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                        360
totagtaggo acagggotoc caggocaggo ctcattetec totggootot aatagtcaat
                                                                        420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt
      <210> 165
     · <211> 195
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (195)
      <223> n = A, T, C or G
      <400> 165
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
                                                                         60
atcogctgtc atcoactatt cettggctag agtaaaaatt attottatag cecatgtece
                                                                        120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
                                                                        180
tcctctgaga tgagt
                                                                        195
      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (383)
      <223> n = A, T, C or G
     <400> 166
acatettagt agtgtggcac atcagggggc catcagggte acagteacte atageetege
                                                                         60
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct
                                                                        120
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt
                                                                        180
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg
                                                                        240
gatgccaacc tcgtctangg tccgtgggaa gctggtgtcc acntcaccta caacctgggc
                                                                        300
gangatetta taaagagget eenagataaa eteeacgaaa ettetetggg agetgetagt
                                                                       360
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```
nggggccttt ttggtgaact ttc
                                                                        383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (247)
      <223> n = A, T, C or G
      <400> 167
acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat
                                                                         60
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aqqccactqc
                                                                        120
tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac
                                                                        180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                        240
tgangtc
                                                                        247
      <210> 168
      <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (273)
      <223> n = A, T, C or G
      <400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa
                                                                         60
aatccctcan cettgttett cacnactgte tatactgana gtgteatgtt tecacaaagg
                                                                        120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                        180
aattcccaac ttccttgcca caagcttccc aggctttctc ccctggaaaa ctccagcttg
                                                                        240
agtcccagat acactcatgg gctgccctgg gca
                                                                        273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (431)
      <223> n = A, T, C or G
      <400> 169
acagcettgg ettecceaaa etceacagte teagtgeaga aagateatet teeageagte
                                                                         60
agctcagacc agggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta
                                                                        120
ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag
                                                                        180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac
                                                                        240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc
                                                                        300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg
                                                                        360
aaagtgatet gataetggat tettaattac etteaaaage ttetggggge cateagetge
                                                                        420
tcgaacactg a
                                                                        431
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
```

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<221> misc_feature
      <222> (1) ... (266)
      <223> n = A,T,C or G
      <400> 170
acctqtqqqc tqqqctqtta tqcctqtqcc qgctqctqaa agggagttca gaggtqgagc
tcaaqqaqct ctqcaqqcat tttqccaanc ctctccanag canagqqaqc aacctacact
                                                                         120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                         180
qtatacttqt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                         240
                                                                         266
tcaaagctag gggtctggca ggtgga
      <210> 171
      <211> 1248
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1248)
      <223> n = A, T, C or G
      <400> 171
                                                                          60
ggcagccaaa tcataaacgg cgaggactgc agcccgcact cgcagccctg gcaggcggca
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg tcagccgcac actgtttcca gaagtgagtg cagagctcct acaccatcgg gctgggcctg
                                                                         120
                                                                         180
cacagtettg aggecgacca agagecaggg agecagatgg tggaggecag ceteteegta
                                                                         240
eggeacecag agtacaacag accettgete getaacgace teatgeteat caagttggae
                                                                         300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc
                                                                         360
geggggaact ettgeetegt ttetggetgg ggtetgetgg egaacggeag aatgeetace
                                                                         420
gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
                                                                         480
                                                                         540
aacggtgact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc
                                                                         600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                         660
                                                                         720
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
attgacccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct
                                                                         780
ccctcaggcc caggagtcca ggccccagc ccctcctccc tcaaaccaag ggtacagatc
                                                                         840
cccagcccct cctcctcag acccaggagt ccagaccccc cagcccctcc tccctcagac
                                                                         900
ccaggagtec ageceetect coetcagace caggagteca gacceeccag eccetectee
                                                                         960
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagccc
                                                                        1020
ccaaccente attecceaga eccagaggte caggteccag eccetentee etcagaccea
                                                                        1080
geggtecaat gecaectaga etnteeetgt acacagtgee eeettgtgge acgttgaece
                                                                        1140
aaccttacca gttggttttt catttttngt ccctttcccc tagatccaga aataaagttt
                                                                        1200
                                                                        1248
<210> 172
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
      <223> Xaa = Any Amino Acid
      <400> 172
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
                 5
                                    10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
            20
                                 25
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
        35
                            40
                                                  45
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
```

```
50
                         55
                                              60
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
                     70
                                          75
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
                 85
                                      90
Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
             100
                                  105
                                                       110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
                             120
                                                  125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                         135
                                              140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
145
                     150
      <210> 173
      <211> 1265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(1265)
      <223> n = A, T, C or G
      <400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
                                                                          60
togggcgtcc tggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc
                                                                         120
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg gtggaggcca gcctctccgt acggcaccca gagtacaaca gacccttgct cgctaacgac
                                                                          180
                                                                          240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg qagcatcagc
                                                                          300
attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg gggtctgctg
gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg
                                                                          420
cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga
                                                                          480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca
                                                                          540
gcatgttetg egeeggegga gggcaagace agaaggacte etgcaaeggt gaetetgggg
                                                                          600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg
                                                                          660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
                                                                         720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                         780
atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag
                                                                         840
tecaggecce cagecectee teceteaae caagggtaca gatececage cecteetece
                                                                         900
tcagacccag gagtccagac ccccagccc ctcctccctc agacccagga gtccagccc
                                                                         960
tecteentca gacceaggag tecagaceee ceageceete eteceteaga eecagggett
                                                                        1020
gaggececca accectecte etteagagte agaggtecaa gececcaace ectegtteee
                                                                        1080
cagacccaga ggtnnaggtc ccagccctc ttccntcaga cccagnggtc caatgccacc
                                                                        1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acceaacctt accaqttggt
                                                                        1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa
                                                                        1260
aaaaa
                                                                        1265
      <210> 174
      <211> 1459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1459)
      <223> n = A, T, C \cdot or G
      <400> 174
ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctqqqcc
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tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg
                                                                         120
tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg
```

```
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcccta
                                                                        240
ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg
                                                                         300
                                                                         360
gtgtgtgtct gccctcttca aggaggtcct ctgcccagtc gcgggggctg acccagagct
                                                                         420
ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tggtgtctga
ngaggtetge antaagetet atgaceeget gtaceacee ancatgttet gegeeggegg
                                                                         480
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact
                                                                        540
                                                                        600
cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag
                                                                        660
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc
                                                                        720
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt
                                                                        780
gacctccacc caatagaaaa teetettata acttttgact ccccaaaaac ctgactagaa
                                                                        840
atagectact gttgacgggg ageettacca ataacataaa tagtegattt atgeatacgt
                                                                        900
tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc
                                                                        960
qtctqtqaat ttttttaaat tqttqcaact ctcctaaaat ttttctqatq tqtttattqa
                                                                        1020
aaaaatccaa qtataaqtqq acttqtqcat tcaaaccaqq qttqttcaaq ggtcaactqt
                                                                        1080
gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa
                                                                       1140
aaatcaagac totacaaaga ggotgggoag ggtggotcat gootgtaato coagcacttt
                                                                       1200
qqqaqqcqaq qcaqqcaqat cacttqaqqt aaggaqttca agaccagcct ggccaaaatq
                                                                       1260
                                                                       1320
qtqaaatcct qtctqtacta aaaatacaaa aqttagctgg atatggtggc aggcgcctgt
aatcccaqct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt
                                                                       1380
gaagtgagtt gagatcacac cactatactc cagctggggc aacagagtaa gactctgtct
                                                                       1440
                                                                       1459
caaaaaaaa aaaaaaaaa
      <210> 175
      <211> 1167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1167)
      <223> n = A, T, C or G
      <400> 175
gegeageect ggeaggegge actggteatg gaaaacgaat tgttetgete gggegteetg
                                                                         60
qtqcatccqc aqtqqqtqct qtcaqccqca cactqtttcc agaactccta caccatcggq
                                                                        120
                                                                        180
ctqqqcctqc acaqtcttqa qqccqaccaa qaqccagqqa gccagatgqt ggaqqccagc
ctctccqtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc
                                                                        240
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag
                                                                        300
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga
                                                                        360
atgectaceg tgctgcactg cgtgaacgtg tcggtggtgt ctgaggangt ctgcagtaag
                                                                        420
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag
                                                                        480
gacteetgea aeggtgacte tggggggeee etgatetgea aegggtaett geagggeett
                                                                        540
                                                                        600
gtgtctttcg gaaaagcccc gtgtggccaa cttggcgtgc caggtgtcta caccaacctc
                                                                        660
tqcaaattca ctgagtggat agagaaaacc gtccagncca gttaactctg gggactggga
                                                                        720
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca
gecetecte ceteaggee aggagteeag gececeagee ceteeteet caaaccaagg gtacagatee ceageceete eteceteaga eccaggagte cagaceeec ageceetent
                                                                        780
                                                                        840
centeagace caggagteca gecetecte enteagacge aggagtecag accececage
                                                                        900
cententecq teagacceaq qqqtgeaqqc ecceaacce tenteentea qaqteaqaqq
                                                                        960
tecaageece caaceeteg ttececagae ceagaggtne aggteecage eceteeteec
                                                                       1020
tragacceag eggteraatg ceacetagan thteeetgta caragtgeer cettgtggea
                                                                       1080
ngttgaccca accttaccag ttggtttttc attttttgtc cctttcccct agatccagaa
                                                                       1140
                                                                       1167
ataaagtnta agagaagcgc aaaaaaa
      <210> 176
      <211> 205
      <212> PRT
      <213> Homo sapien
      <220>
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<221> VARIANT

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<222> (1)...(205)
       <223> Xaa = Any Amino Acid
       <400> 176
 Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                                       10
 Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
             20
                                  25
 Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
         35
                              40
 Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu
                          55
                                               60
 Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                      70
                                           75
 Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                                      90
 Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
             100
                                  105
                                                       110
 Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
         115
                              120
                                                   125
 Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
     130
                          135
 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
 145
                      150
                                          155
                                                               160
 Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
                 165
                                      170
                                                           175
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
             180
                                  185
 Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
       <210> 177
       <211> 1119
       <212> DNA
       <213> Homo sapien
       <400> 177
 gcgcactcgc agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc
                                                                           60
 gtectggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc
                                                                          120
 ategggetgg geetgeacag tettgaggee gaecaagage cagggageea gatggtggag
                                                                          180
 gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg
                                                                          240
 ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct
                                                                          300
 tegeagtgee ctacegeggg gaactettge etegtttetg getggggtet getggegaac
                                                                          360
 gatgCtgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc
                                                                          420
caaccetgge agggttgtac cattleggea acttecagtg caaggacgte etgetgeate
                                                                          480
 ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag
                                                                          540
caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt
                                                                          600
actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc cagttatcct cactgaattg agatttcctg cttcagtgtc agccattccc acataatttc
                                                                          660
                                                                          720
tgacctacag aggtgaggga tcatataget etteaaggat getggtaete eeeteacaa
                                                                          780
 ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca
                                                                          840
ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg
                                                                          900
ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca
                                                                          960
accacctcag gactcctgga ttctctgcct agttgagctc ctqcatqctq cctccttqqq
                                                                         1020
 gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc
                                                                         1080
 ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa
                                                                         1119
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<210> 178 <211> 164

<212> PRT

<213> Homo sapien

<223> n = A, T, C or G

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<220>
      <221> VARIANT
      <222> (1)...(164)
      <223> Xaa = Any Amino Acid
      <400> 178
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                                     10
                                                         15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
            20
                                25
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                                                 45
                            40
        35
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
                        55
                                             60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                                         75
                    70
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85
                                     90
                                                         95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
            100
                                105
                                                     110
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
        115
                            120
                                                 125
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
                                             140
    130
                        135
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Thr Ala Ser
Pro Gly Thr Leu
      <210> 179
      <211> 250
      <212> DNA
      <213> Homo sapien
      <400> 179
                                                                        60
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
ccagetgeec eeggeegggg gatgegagge teggageace ettgeeegge tgtgattget
                                                                        120
qccaqqcact qttcatctca qcttttctgt ccctttgctc ccggcaagcg cttctgctga
                                                                        180
                                                                        240
aagttcatat ctqqaqcctq atqtcttaac qaataaaggt cccatgctcc acccqaaaaa
                                                                        250
aaaaaaaaa
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
                                                                         60
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                        120
teacceagae ecegeceetg ecegtgeece aegetgetge taacgacagt atgatgetta
                                                                        180
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
tgatttaaaa aaaaaaaaa aa
                                                                        202
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (558)
```

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<400> 181
tccytttgkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcyngg
aatgittagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct
                                                                         120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                         180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca
                                                                         240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                         300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa
                                                                         360
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw
                                                                         420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt
                                                                         480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                         540
caaaaaaaa aaaaaaaa
                                                                         558
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(479)
      <223> n = A, T, C or G
      <400> 182
acagggwttk grggatgeta agsccccrga rwtygtttga tecaaccetg gettwtttte
                                                                          60
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtg gcacccctgg
                                                                         120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg
                                                                         180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                         240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
                                                                         300
                                                                         360
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara
                                                                         420
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaaa
                                                                         479
      <210> 183
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 183
aggegggage agaagetaaa geeaaageee aagaagagtg geagtgeeag eactggtgee
                                                                          60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                         120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
                                                                         180
gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat
                                                                         240
tgttaatcct gccagtcttt ctcttcaagc cagggtgcat cctcagaaac ctactcaaca
                                                                         300
cagcactcta ggcagccact atcaatcaat tqaaqttqac actctgcatt aratctattt
                                                                         360
gccatttcaa aaaaaaaaaa aaaa
                                                                         384
      <210> 184
      <211> 496
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (496)
      <223> n = A,T,C or G
      <400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc
                                                                          60
agggagateg agtetataeg etgaagaaat ttgaceegat gggacaacag acetgeteag
                                                                         120
cocatecte tegettete ccagatgaca aatactetsg acacegaate accateaaga
                                                                         180
aacgettcaa qqtqctcatq acccaqcaac cqcqcctqt cctctqaqqq tcccttaaac
                                                                         240
tgatgtcttt tctgccacct gttacccctc ggagactccg taaccaaact cttcggactg
                                                                         300
```

```
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                        360
attatgettg tgtgaggeaa teatggtgge ateacceata aagggaacae atttgaettt
                                                                        420
                                                                        480
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                        496
taaaaaaaa aaaaaa
      <210> 185
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 185
qctqqtagcc tatggcqkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
                                                                         60
caaqtatcyt gegesgegte ttetacegte cetacetgea gatetteggg cagatteece
                                                                        120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct
                                                                        180
qqqcacaccc tcctqqqqcc caqqcqqqca cctqcqtctc ccaqtatqcc aactqqctqq
                                                                        240
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca
                                                                        300
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                        360
gcgcagcgtt accgcctcat ccgg
                                                                        384
      <210> 186
      <211> 577
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (577)
      <223> n = A, T, C or G
qaqttaqctc ctccacaacc ttgatgaggt cgtctqcagt ggcctctcgc ttcataccqc
                                                                         60
thecategte atactgtagg tttgccacca cytectggca tettggggeg gentaatatt
                                                                        120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc
                                                                        180
teggtgtgaa aggateteee agaaggagtg etegatette eccaeaettt tgatgaettt
                                                                        240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                        300
caqccctatc atgccqttqa mcqtqccqaa qarcaccqaq ccttqtqtqq qqqkkqaaqt
                                                                        360
cteacceaqa ttetqeatta ceaqaqaqee qtqqeaaaaq acattgacaa actegeecaq
                                                                        420
qtqqaaaaaq amcamctcct gqarqtgctn gccqctcctc gtcmgttggt ggcagcgctw
                                                                        480
teettttgae acacaaacaa gttaaaggea tttteageee ecagaaantt gteateatee
                                                                        540
aagatntcgc acagcactna tccagttggg attaaat
                                                                        577
      <210> 187
      <211> 534
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (534)
      <223> n = A, T, C or G
      <400> 187
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw
                                                                        60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                       120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta
                                                                       180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat ctttttttt
                                                                       240
gacacaagto ogaaaaaago aaaagtaaac agttatyaat ttgttagoca attcacttto
                                                                       300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                       360
tgatatttga gcggaagagt agcetttcta cttcaccaga cacaactccc tttcatattg
                                                                       420
ggatgttnac naaagtwatg tototwacag atgggatget tttgtggcaa ttctgttctg
                                                                       480
aggatetece agtttattta ceaettgeae aagaaggegt tttetteete agge
                                                                       534
```

```
<210> 188
      <211> 761
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (761)
      <223> n = A, T, C or G
      <400> 188
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                         60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                        120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                        180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                        240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                        300
ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa
                                                                        360
acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                       420
gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgttttttt tatnataaaa
                                                                        480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa
                                                                       540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
                                                                       600
atgcttaatt cacaaatgct aatttcatta taaatgtttg ctaaaataca ctttgaacta
                                                                       660
tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac
                                                                       720
gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                       761
      <210> 189
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (482)
      <223> n = A, T, C or G
      <400> 189
ttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccqca
                                                                        60
caccggggct atnagaagca agaaggaagg agggagggca cagcccttg ctgagcaaca
                                                                       120
aagccgcctg ctgccttctc tgtctgtctc ctggtgcagg cacatgggga gaccttcccc
                                                                       180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
                                                                       240
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                       300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
                                                                       360
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg
                                                                       420
gttcggcca gctccncgtc caaaaantat tcacccnnct ccnaattgct tgcnggnccc
                                                                       480
CC
                                                                       482
      <210> 190
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(471)
      <223> n = A, T, C or G
      <400> 190
tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg
                                                                        60
aaaactotog catocagtga gaactaccat acaccacatt acagotngga atginotoca
                                                                       120
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacq aaaqaacaaq
                                                                       180
cgcttttgac atacaatgca caaaaaaaa agggggggg gaccacatgg attaaaattt
                                                                       240
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
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tqaaaaattt catqtatqca atccaaccaa agaacttnat tggtgatcat gantnctcta 360 ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa 420 totgtaattn anttcaacct cogtacngaa aaatnttnnt tatacactcc c 471 <210> 191 <211> 402 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (402) <223> n = A, T, C or G<400> 191 qaqqqattqa aqqtctqttc tastqtcggm ctgttcagcc accaactcta acaagttgct 60 gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa 120 180 attetteace agteacatet tetaggacet ttttggatte agttagtata agetetteca 240 cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg 300 ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc ctttgtgcat ccattttaaa tatacttaat agggcattgk incactaggt taaattctgc 360 aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca 402 <210> 192 <211> 601 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1) ... (601) <223> n = A, T, C or G<400> 192 gageteggat ecaataatet ttgtetgagg geageacaea tatneagtge eatggnaact 60 ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120 180 atqcytyttt qaytaccqtq tgccaagtgc tggtgattct yaacacacyt ccatcccgyt cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc 240 acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac 300 cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga 360 tacatetect gacagtactg aagaacttet tettttgttt caaaageare tettggtgee 420 tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac 480 aaaacattqc qatttqaqqc tcaqcaacag caaatcctqt tccggcattg gctgcaagag 540 cetegatgta geeggeeage geeaaggeag gegeegtgag eeccaceage ageagaagea 600 601 q <210> 193 <211> 608 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(608) <223> n = A, T, C or G<400> 193 atacagecca nateccaeca egaagatgeg ettgttgaet gagaacetga tgeggteaet 60 qqtcccqctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt 120 cccaacqcaq gcaqmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg 180 240 tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc

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agaaccttcc gcctgttctc tggcgtcacc tgcagctgct gccgctgaca ctcggcctcg
                                                                           360
gaccagogga caaacggort tgaacagoog cacctcacgg atgoocagtg tqtcqcqctc
                                                                           420
caggammasc accadegtgt ccaggtcaat gteggtgaag ceeteegegg gtratggegt
                                                                           480
ctgcagtgtt tttgtcgatg ttctccaggc acaggctggc cagctgcqgt tcatcqaaqa
                                                                           540
gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggctcg cagttcttct tcaggaactc
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cacgcaat
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      <223> n = A, T, C or G
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                                                                          120
tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg
                                                                          180
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac
                                                                          240
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt
                                                                          300
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg
                                                                          360
aaataaatat agttattaaa ggttgtcant cc
                                                                          392
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      <211> 502
      <212> DNA
      <213> Homo sapien
      <221> misc feature
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      \langle 223 \rangle n = A.T.C or G
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ccgagctgag gcagatgttc ccacagtgac ccccaqagcc stgggstata gtytctgacc
                                                                          120
cetencaagg aaagaccaes ttetggggae atgggetgga gggeaggaee tagaggeaee
                                                                          180
aagggaaggc cccattccgg ggstgttccc cgaggaggaa gggaagggc tctgtgtgcc ccccasgagg aagaggcct gagtcctggg atcagacacc ccttcacgtg tatccccaca
                                                                          240
                                                                          300
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact
                                                                          360
gscscacacc cacccagage acgccacccg ccatggggar tgtgctcaag gartegengg
                                                                          420
gcarcqtgga catctngtcc caqaaqqqqq caqaatctcc aataqanqqa ctqarcmstt
                                                                          480
gctnanaaaa aaaaanaaaa aa
                                                                          502
      <210> 196
      <211> 665
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(665)
      <223> n = A, T, C or G
      <400> 196
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                                                                           60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                          120
wagetgtttk gagttgatts geaccactge acceacact teaatatgaa aacyawttga
                                                                          180
actwatttat tatettgtga aaagtataac aatgaaaatt ttgttcatac tgtattkatc
                                                                          240
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aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt
                                                                        300 -
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact
                                                                        360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                        420
watatttatt toattaatit otttootkgt ttacgtwaat tttgaaaaga wtgcatgatt
                                                                        480
tcttgacaga aatcgatctt gatgctgtgg aagtagtttg acccacatcc ctatgagttt
                                                                        540
ttcttaqaat qtataaaqqt tqtaqcccat cnaacttcaa agaaaaaaat gaccacatac
                                                                        600
tttqcaatca qqctqaaatq tqqcatqctn ttctaattcc aactttataa actaqcaaan
                                                                        660
aagtg
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      <211> 492
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      <222> (1) ... (492)
      <223> n = A, T, C or G
      <400> 197
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atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                        120
aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag
                                                                        180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
                                                                        240
caaaattota cootqaaact tactocatoo aaatattgga ataanagtoa goagtgatac
                                                                        300
attetettet qaaetttaga tittetagaa aaatatgtaa tagtgateag gaagagetet
                                                                        360
tqttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                        420
cattleacte ceateacggg agteaatget acctgggaca cttgtatttt gtteatnetg
                                                                        480
ancntggctt aa
                                                                        492
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (478)
      <223> n = A, T, C \text{ or } G
      <400> 198
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tqtntccacn acaaatcatn ttacntnaqt aagaqqccan ctacattqta caacatacac
                                                                        120
                                                                        180
tgagtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat
                                                                        240
natatatgic aatongattt aagatacaaa acagatocta tggtacatan catcntgtag
                                                                        300
qaqttqtqqc tttatqttta ctgaaagtca atgcaqttcc tqtacaaaga gatggccgta
                                                                        360
agcattctag tacctctact ccatggttaa gaatcgtaca cttatgttta catatgtnca
                                                                        420
qqqtaaqaat tqtqttaaqt naanttatqq aqaqqtccan qaqaaaaatt tqatncaa
                                                                        478
      <210> 199
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (482)
      <223> n = A,T,C or G
      <400> 199
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                                                                        60
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tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca
                                                                     120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                     180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                     240
tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga
                                                                     300
aaatttacct ggangaaaag aggettingg etggggacca teccattgaa eettetetta
                                                                     360
anggacttta agaanaaact accacatgtn tgtngtatcc tgqtgccngg ccgtttantq
                                                                     420
aacntngach neaccettht ggaatanant ettgaengen teetgaactt geteetetge
                                                                     480
                                                                     482
      <210> 200
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
      <400> 200
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cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                    120
aaggctgagc tgacgccgca gaggtcgtgt cacgtcccac gaccttgacg ccgtcgggga
                                                                    180
cagcoggaac agagcooggt gaangoggga ggcotogggg agcocotogg gaagggoggo
                                                                     240
ccgagagata cgcaggtgca ggtggccqcc
                                                                    270
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     <211> 419
     <212> DNA
      <213> Homo sapien
     <221> misc feature
     <222> (1)...(419)
     <223> n = A, T, C or G
     <400> 201
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gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg
                                                                    120
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
                                                                    180
tggagtgggt gcaccctccc tgtagaacct ggttacnaaa gcttggggca gttcacctgg
                                                                    240
tctgtgaccg tcattttctt gacatcaatg ttattagaag tcaggatatc ttttagagag
                                                                    300
tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga
                                                                    360
aaaaqttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                    419
     <210> 202
     <211> 509
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(509)
     <223> n = A, T, C or G
     <400> 202
60
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
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gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa
                                                                    180
tacnoncaaa aatcaaaaat atacntntot ttoagcaaac ttngttacat aaattaaaaa
                                                                    240
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
                                                                    300
ggaactaaaa taaaaaaaaa cactnccgca aaggttaaag ggaacaacaa attcntttta
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caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                            420
qqatcttaac ttttactnca ctttqtttat ttttttanaa ccattqtntt qqqcccaaca
                                                                            480
                                                                            509
caatggnaat nccnccncnc tggactagt
       <210> 203
       <211> 583
       <212> DNA
       <213> Homo sapien
      <220>
       <221> misc_feature
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\langle 223 \rangle n = A,T,C or G
      <400> 203
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tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac
                                                                            120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                            180
gaaaatette tetagetett ttgactgtaa attittgact ettgtaaaac atccaaatte
                                                                            240
attittettg tetttaaaat tatetaatet tieeattitt teeetatiee aagteaatti
                                                                            300
gettetetag ceteatttee tagetettat etaetattag taagtggett tttteetaaa
                                                                            360
                                                                            420
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                            480
tocattttag toactaaacg atatonaaag tgocagaatg caaaaggttt gtgaacattt attcaaaagc taatataaga tatttcacat actcatcttt ctg
                                                                            540
                                                                            583
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      <211> 589
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
      <400> 204
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tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                            120
aatotottat gotatatoat attttaagtt aaactaatga gtoactggot tatottotoo
                                                                            180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
                                                                            240
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt
                                                                            300
attiticatgo aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag
                                                                            360
cattacaaaa ctqctcaaat tqtttqttaa qnttatccat tataattaqt tnqqcaqqaq
                                                                            420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc
                                                                            480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat ttattnagaa tgaattcaca tgttattatt ccntagccca acacaatgg
                                                                            540
                                                                            589
      <210> 205
      <211> 545
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A, T, C \text{ or } G
      <400> 205
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agaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata
                                                                            120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
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ttaagatcat agagcttgta agtgaaaaga taaaatttga cctcagaaac tctgagcatt
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aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                         300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                         360
tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                         420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg
                                                                         480
aaggattaga tatgttteet ttgecaatat taaaaaaata ataatgttta etaetagtga
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aaccc
                                                                         545
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      <211> 487
      <212> DNA
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      <221> misc_feature
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catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna
                                                                        120
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtqqatqtqt
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cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac
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actqctqcaa acqctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag
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ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt
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tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cggtggcaag
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aactottega accgetteet caaaggenge tgecacattt gtggentetn ttgeacttgt
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ttcaaaa
                                                                        487
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      <221> misc_feature
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      <400> 207
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                                                                        120
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana
                                                                        180
atctttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca
                                                                        240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggq tqqqacatqq
                                                                        300
aaaagaaggc agcctaggcc ctggggagcc ca
                                                                        332
      <210> 208
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(524)
      <223> n = A, T, C or G
      <400> 208
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
                                                                         60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcaq agtqactgat
                                                                        120
tttaaaggac atggagettg teacaatgte acaatgteac agtgtgaagg geacacteac
                                                                        180
tecegegtga tteacattta geaaceaaca atageteatg agtecatact tgtaaatact
                                                                        240
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tttggcagaa tacttnttga aacttgcaga.tgataactaa gatccaagat atttcccaaa
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gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc
                                                                        360
atgageccag acactgaeat caaactaage ceaettagae teeteaceae cagtetgtee
                                                                        420
tqtcatcaqa caqqaqqctq tcaccttqac caaattctca ccaqtcaatc atctatccaa
                                                                        480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                        524
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      <211> 159
      <212> DNA
      <213> Homo sapien
      <400> 209
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                                                                         60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca
                                                                        120
                                                                        159
caaaggacto togaccoaaa otgoccoaga coototoca
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      <211> 256
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(256)
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      <400> 210
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actgaatttc tttccacttq qactattaca tgccanttga qqqactaatq gaaaaacgta
                                                                        120
                                                                        180
tqqqqaqatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca
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ccaggatgct aaatca
                                                                        256
      <210> 211
      <211> 264
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(264)
      <223> n = A, T, C or G
      <400> 211
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                                                                       120
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                       180
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
ggggagatac attongaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
                                                                       240
                                                                       264
aaaaaaqqaq caaatgagaa gcct
      <210> 212
      <211> 328
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (328)
      <223> n = A, T, C or G
      <400> 212
acccaaaaat ccaatgctga atatttggct tcattattcc canattcttt gattgtcaaa
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```
ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag
                                                                                                                                                  120
 gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag
                                                                                                                                                  180
 ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta
                                                                                                                                                  240
 cccctacnac tetttactet etgganaggg ccagtggtgg tagetataag ettggecaca
                                                                                                                                                  300
 ttttttttc ctttattcct ttgtcaga
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             <210> 213
             <211> 250
             <212> DNA
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             <220>
             <221> misc_feature
             <222> (1) ... (250)
             <223> n = A, T, C or G
             <400> 213
acttatgage agagegacat atcenagtgt agactgaata aaactgaatt etetecagtt
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taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                                                                                                  120
cattatgcca aagganatat acatttcaat totccaaact tottcctcat tocaagagtt
                                                                                                                                                  180
 ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct
                                                                                                                                                  240
tctcatcqqt
                                                                                                                                                  250
             <210> 214
            <211> 444
             <212> DNA
            <213> Homo sapien
            <220>
            <221> misc feature
            <222> (1) ... (444)
            <223> n = A, T, C or G
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                                                                                                                                                    60
gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg
                                                                                                                                                  120
tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt
                                                                                                                                                  180
tgaatttcat toccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac
                                                                                                                                                  240
contacgant officers to the contact of the contact o
                                                                                                                                                  300
ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag
                                                                                                                                                  360
agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt
                                                                                                                                                  420
actttqctct ccctaatata cctc
                                                                                                                                                  444
            <210> 215
            <211> 366
            <212> DNA
            <213> Homo sapien
            <220>
            <221> misc feature
            <222> (1)...(366)
            <223> n = A, T, C or G
            <400> 215
acttatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt
                                                                                                                                                   60
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                                                                                                 120
cattatgcca aagganatat acatttcaat totocaaact tottoctcat tocaagagtt
                                                                                                                                                 180
ttcaatattt qcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct
                                                                                                                                                 240
tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa
                                                                                                                                                 300
tocaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt
                                                                                                                                                 360
ggtgcc
                                                                                                                                                 366
```

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<210> 216
      <211> 260
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(260)
      <223> n = A, T, C or G
      <400> 216
ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc
                                                                            60
caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc atttttttat
                                                                           120
taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa
                                                                            180
atcaaaaatt tootnaagtt ntcaaqotat catatatact ntatootgaa aaagcaacat
                                                                            240
aattetteet teeeteettt
                                                                            260
      <210> 217
      <211> 262
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (262)
      <223> n = A, T, C or G
      <400> 217
acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta
                                                                            60
tcttgcctat aattttctat tttaataagg aaatagcaaa ttggggtggg gggaatgtag
                                                                           120
ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt
                                                                           180
atgaataatc tgtatgatta tatgtctcta qagtagattt ataattagcc acttacccta
                                                                           240
                                                                           262
atatccttca tgcttgtaaa gt
      <210> 218
      <211> 205
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (205)
      <223> n = A, T, C or G
      <400> 218
accaaggtgg tgcattaccg gaantggatc aangacacca tcgtggccaa cccctgagca cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaagactc
                                                                            60
                                                                           120
aggeotoccc agttotactg acctttgtcc ttangtntna ngtocagggt tgctaggaaa
                                                                           180
                                                                           205
anaaatcagc agacacaggt gtaaa
      <210> 219
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 219
tactgttttg tctcagtaac aataaataca aaaagactgg ttgtgttccg gccccatcca
                                                                            60
accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga
                                                                           114
      <210> 220
      <211> 93
      <212> DNA
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<213> Homo sapien
      <400> 220
actagccagc acaaaaqqca qqqtaqcctq aattqctttc tqctctttac atttctttta
                                                                         60
aaataagcat ttagtgctca gtccctactg agt
                                                                         93
      <210> 221
      <211> 167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (167)
      <223> n = A, T, C or G
      <400> 221
actangtgca ggtgcgcaca aatatttgtc gatattccct tcatcttgga ttccatgagg
                                                                        60
tettttgccc ageetgtggc tetactgtag taagtttetg etgatgagga geeagnatge
                                                                       120
ccccactac cttccctgac gctccccana aatcacccaa cctctgt
                                                                      . 167
      <210> 222
      <211> 351
      <212> DNA
      <213> Homo sapien
      <400> 222
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                                                                        60
gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa
                                                                       120
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa
                                                                       180
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt
                                                                       240
taggtgagca tgattagaga gcttgtaggt tgcttttaca tatatctggc atatttgagt
                                                                       300
ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t
                                                                       351
      <210> 223
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (383)
      <223> n = A, T, C or G
aaaacaaaca aacaaaaaaa acaattette atteagaaaa attatettag qqaetqatat
tggtaattat ggtcaattta atwrtrttkt ggggcatttc cttacattgt cttgacaaga
                                                                       120
ttaaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc
                                                                       180
tgccaaagga agtctaagga attagtagtg ttcccmtcac ttgtttggag tgtgctattc
                                                                       240
taaaagattt tgatttcctg gaatgacaat tatattttaa ctttggtggg ggaaanagtt
                                                                       300
ataggaccac agtottoact totgatactt gtaaattaat ottttattgc acttgttttg
                                                                       360
accattaagc tatatgttta aaa
                                                                       383
      <210> 224
      <211> 320
      <212> DNA
      <213> Homo sapien
      <400> 224
cccctgaagg cttcttgtta gaaaatagta cagttacaac caataggaac aacaaaaaga
                                                                        60
aaaagtttgt gacattgtag tagggagtgt gtacccctta ctccccatca aaaaaaaaat
                                                                       120
ggatacatgg ttaaaggata raagggcaat attttatcat atgttctaaa agagaaggaa
                                                                       180
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gagaaaatac tactttctcr aaatggaagc ccttaaaggt gctttgatac tgaaggacac
                                                                       240
aaatqtqqcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgcagt
                                                                       300
tttaractcm gcattgtgac
                                                                       320
      <210> 225
      <211> 1214
      <212> DNA
      <213> Homo sapien
      <400> 225
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ttctqctcqq gcqtcctggt gcatccgcag tgggtgctgt cagccgcaca ctgtttccag
                                                                       120
aactectaca ccateggget gggeetgeac agtettgagg ccgaccaaga gecagggage
                                                                       180
cagatggtgg aggccagcct ctccgtacgg cacccagagt acaacagacc cttgctcgct
                                                                       240
aacqacctca tgctcatcaa gttggacgaa tccgtgtccg agtctgacac catccggagc
                                                                       300
atcagcattg cttcgcagtg ccctaccgcg gggaactctt gcctcgtttc tggctggggt
                                                                       360
ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaacgtgtc ggtggtgtct
                                                                       420
gaggaggtet geagtaaget etatgaceeg etgtaceace ceageatgtt etgegeegge
                                                                       480
ggagggcaag accagaagga ctcctgcaac ggtgactctg gggggcccct gatctgcaac
                                                                       540
gggtacttgc agggccttgt gtctttcgga aaagccccgt gtggccaagt tggcgtgcca
                                                                       600
ggtgtctaca ccaacctctg caaattcact gagtggatag agaaaaccgt ccaggccagt
                                                                       660
                                                                       720
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caggaatate tgtteceage eceteetee teaggeceag gagtecagge ececagece teeteetea aaccaagggt acagateee ageceeteet eceteagace caggagteca
                                                                       780
                                                                       840
gacccccag ccctcctcc ctcagaccca ggagtccagc ccctcctccc tcagacccaq
                                                                       900
gagtecagae eccecagece etectecete agacecaggg gtecaggece ecaacecete
                                                                       960
ctccctcaga ctcagaggtc caagccccca acccctcctt ccccagaccc agaggtccag
                                                                      1020
gteccagece etectecete agacecageg gtecaatgee acetagaete tecetgtaca
                                                                      1080
cagtgccccc ttgtggcacg ttgacccaac cttaccagtt ggtttttcat tttttgtccc
                                                                      1140
1200
aaaaaaaaa aaaa
                                                                      1214
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      <211> 119
      <212> DNA
      <213> Homo sapien
      <400> 226
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agaacctggc ccaqtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt
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      <210> 227
      <211> 818
      <212> DNA
      <213> Homo sapien
      <400> 227
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                                                                       120
acqqacqqtt cttaqcacaa tttqtqaaat ctqtqtaraa ccqqqctttq caqqqqaqat
                                                                       180
aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta
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gagaaagcca cgctcggcct tctctgaacc aggatggaac ggcagacccc tgaaaacgaa
                                                                       300
gettgteece ttecaateag ceaettetga gaaceeceat etaaetteet aetggaaaag
                                                                       360
agggeeteet caggageagt ecaagagttt teaaagataa egtgaeaact accatetaga
                                                                       420
ggaaagggtg caccetcage agagaageeg agagettaac tetggtegtt tecagagaca
                                                                       480
acctqctqqc tqtcttqqqa tqcqcccaqc ctttqaqaqq ccactacccc atqaacttct
                                                                       540
qccatccact qqacatqaaq ctqaqqacac tqqqcttcaa cactqaqttq tcatqaqaqq
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                                                                       660
gacaggetet geetteaage eggetgaggg eageaaceae teteeteece ttteteaege
aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggct
                                                                       720
caagaggata tgaggactgt ctcagcctgg ctttgggctg acaccatgca cacacacaag
                                                                       780
                                                                       818
gtccacttct aggttttcag cctagatggg agtcgtgt
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<210> 228
      <211> 744
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      <213> Homo sapien
      <400> 228
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gtcatgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagaccgtgt
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togtggccga cotggcctct cotggcctgt ttottaagat goggagtcac atttcaatgg
                                                                       180
taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga
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tgctcggtgc acattggggt gctttgggat aaaagattta tgagccaact attctctggc
                                                                       300
accagattet aggecagttt gttecaetga agetttteee acageagtee acetetgeag
                                                                       360
gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt
                                                                       420
gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg
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ccagacggtg ttggccactc ccttctaaaa cacaggcgcc ctcctggtga cagtgacccg
                                                                       540
cogtggtatg cottggccca ttocagcagt cocagttatg catttcaagt ttggggtttg
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ttcttttcgt taatgttcct ctgtgttgtc agctgtcttc atttcctggg ctaagcagca
                                                                       660
ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt
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cttcactctg aagtagctgg tggt
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cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc
                                                                       120
tgcagggttg ttgtttttta attattattg ttagaaacgt caccacagt ccctgttaat
                                                                       180
ttgtatgtga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagtct
                                                                       240
cactaggete etecttgeee teacactgga gteteegeea gtgtgggtge ecactgaeat
                                                                       300
      <210> 230
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 230
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                                                                        60
gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg
                                                                       120
caatataaag tootggttoa cactoaggaa cgagagotga cocagttaag ggagaagttg
                                                                       180
egggaaggga gagatgeete eeteteattg aatgageate teeaggeeet eeteacteeg
                                                                       240
gatgaaccgg acaagteeca ggggcaggac etecaagaaa cagacetegg eegegaccae
                                                                       300
                                                                       301
      <210> 231
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 231
gcaagcacgc tggcaaatct ctgtcaggtc agctccagag aagccattag tcattttagc
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caggaactcc aagtccacat ccttggcaac tggggacttg cqcaggttag ccttgaggat
                                                                       120
ggcaacacgg gacttctcat caggaagtgg gatgtagatg agctgatcaa gacggccagg
                                                                       180
tetgaggatg geaggateaa tgatgteagg eeggttggta eegecaatga tgaacacatt
                                                                       240
ttttttgtg gacatgccat ccatttctgt caggatctgg ttgatgactc ggtcagcagc
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                                                                       301
      <210> 232
      <211> 301
      <212> DNA
      <213> Homo sapien
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<211 <212	> 233 > 301 > DNA > Homo sapi	en				
atgactgact atgctaaggc cctagaagtt gagtagctgg	cccagagatc acagagcatc gactacaggc	gctctctaag gtttgatcca tagctggtgc acacagtcac gtagagactt	accetettat getggcacce tgaagcagge	tttcagaggg ctggcctcac cctgttagca	gaaaatgggg acagactccc attctatgcg	60 120 180 240 300 301
<211 <212	> 234 > 301 > DNA > Homo sapid	en				
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<211: <212:	> 235 > 283 > DNA > Homo sapie	en				
tggggctgtg aattccctca tgctttcact atgttatctt	tcttttaggg aatgtctctg tgaactgatg	gtttgagaaa aatcatttac aacttctgtc ctcataggag tagatttaag	caggtttgga cctctttgtt agaatataag	gaggattcag catggatagt aactctgagt	acagctcagg ccaataaata	60 120 180 240 283
<2112 <2122	> 236 > 301 > DNA > Homo sapie	en				
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<210> 237 <211> 301

<211> 301

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       <213> Homo sapien
      <400> 237
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actcaatttt tgttcgctcc tttttggcct tttccaattt gtccatctca attttctggg
                                                                          120
ccttggctaa tgcctcatag taggagtcct cagaccagcc atggggatca aacatatcct
                                                                          180
ttgggtagtt ggtgccaagc tcgtcaatgg cacagaatgg atcagcttct cgtaaatcta
                                                                          240
gggttccgaa attettett cetttggata atgtagttca tatecattce etcetttate
                                                                          300
                                                                          301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 238
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                                                                           60
gttcacagtt cagcccctg ctcagaaaac caacgggcca gctaaggaga ggaggaggca
                                                                          120
ccttgagact tccggagtcg aggctctcca gggttcccca gcccatcaat cattttctgc
                                                                          180
accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca
                                                                          240
gtgtgggacc cagggtctgt tcttcacagt aggaggtgga agggatgact aatttcttta
                                                                          300
                                                                          301
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      <211> 239
      <212> DNA
      <213> Homo sapien
      <400> 239
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ttctgtcaaa ccatgatact gagctttgtg acaacccaga aataactaag agaaggcaaa
                                                                          120
cataatacct tagagatcaa gaaacattta cacagttcaa ctqtttaaaa atagctcaac
                                                                         180
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      <211> 300
      <212> DNA
      <213> Homo sapien
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gggatetgee etceagtgga acettttaag gaagaagtgg geecaageta agtteeacat
                                                                         120
gctgggtgag ccagatgact tctgttccct ggtcactttc ttcaatgggg cgaatgggg ctgccaggtt tttaaaatca tgcttcatct tgaagcacac ggtcacttca ccctcctcac
                                                                         180
                                                                         240
gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatqtc
                                                                         300
      <210> 241
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 241
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cctctttgga ggaaactcca gcagctatgt tqqtqtctct gagggaatgc aacaaqqctq
                                                                         120
ctcctccatg tattggaaaa ctgcaaactg gactcaactg gaaggaagtg ctgctgccag
                                                                         180
tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtctttct
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tectectect greatacggt eteteteaag cateetttgt tgteagggge etaaaaggga
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<212> DNA
      <213> Homo sapien
      <400> 242
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                                                                        60
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                                                                       120
qtcttcaaqa atatatcatt cctttttcac tagaacccat tcaaaatata agtcaagaat
                                                                       180
cttaatatca acaaatatat caaqcaaact ggaaggcaga ataactacca taatttaqta
                                                                       240
taaqtaccca aagttttata aatcaaaagc cctaatgata accattttta gaattcaatc
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                                                                       301
      <210> 243
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 243
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ggtggcccaa gctatgaaat cagagggagg cttcatctgg gcctgtaaaa actatgatgg
                                                                       120
tgacgtgcag toggactotg tggcccaagg gtatggctot otoggcatga tgaccagogt
                                                                       180
gctggtttgt ccagatggca agacagtaga agcagaggct gcccacggga ctgtaacccg
                                                                       240
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                                                                       120
ccagggacct tqqaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa
                                                                       180
                                                                       240
aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca
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                                                                       120
aaqqccaqqa qatattqtca ttaatqtara cttcaqqaca ctaqaqtata qcaqccctat
                                                                       180
                                                                       240
gttttcaaag agcagagatg caattaaata ttgtttagca tcaaaaaggc cactcaatac
agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa
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                                                                       301
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                                                                       180
agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac
                                                                       240
taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc
caaatqtqtc ttacaaaaca cgttcctaac aaggtatqct ttacactacc aatqcaqaaa
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gtgtcctgtg ttcaggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc
                                                                          180
ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc
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cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta
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acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag
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gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag
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ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc
                                                                          180
catcgtaatg aattattttg aaaattaatt ccaccatcct ttcagattct ggatggaaag
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actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt
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cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac
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ctaaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaaqacta
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caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat qattqaaacc
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      <211> 301
      <212> DNA
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                                                                          120
                                                                          180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa
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cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct
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      <211> 301
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                                                                          120
tcattccttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa
                                                                          180
atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt
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caactaaaaa aaaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct
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tqqtctqatt qttttcaqac cttaaaatat aaacttqttt cacaagcttt aatccatgtg
                                                                          180
gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt
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tocatagtgo coacagggta ttoctoacat tttotocata ggaaaatgot ttttoccaag
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                                                                          120
                                                                          180
                                                                          240
gaaaaaaata aagetttgga etttteaagg ttgettaaca ggtaetgaaa gaetggeete
acttaaactq aqccaggaaa aqctqcaqat ttattaatqq qtqtqttaqt gtqcaqtqcc
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      <212> DNA
      <213> Homo sapien
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tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtaggggg
                                                                         180
aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta
                                                                         240
                                                                          300
aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac
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aa
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acceccaaaa geetggacae ettgageaca eagttatgae eaggacagae teatetetat
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aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt
                                                                        240
gtggcctctc ggcctggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt
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                                                                        301
      <210> 257
      <211> 301
      <212> DNA
      <213> Homo sapien
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tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat
                                                                        180
gtcacattac tcccttcagt gatttcttgt agaagtgcca atccctgaat gccaccaaga
                                                                        240
tettaatett cacatettta atettatete tttgacteet etttacaceg gagaaggete
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      <211> 301
      <212> DNA
      <213> Homo sapien
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      <222> (1) ... (301)
      <223> n = A, T, C or G
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cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaaqat cttaacactg
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atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctqtatq qtqqtqtcat
                                                                        240
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac
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      <211> 301
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gcaaaqccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt
                                                                        180
tocageteae ateteatetg catgeageae ggaceggatg egeceaetgg gtettggett
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coctcocate ttctcaagca gtgtccttgt tgagccattt gcatccttgg ctccaggtgg
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aqaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac
                                                                        180
tagggcaaaa taaataagig tgiggaagcc cigataagig citaataaac agactgattc
                                                                        240
actgagacat cagtacetge cegggeggee getegageeg aattetgeag atateeatea
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                                                                        301
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agcaccaact attocataca attoatcago aggaaataaa ggotottoag aaggttoaat
                                                                        180
ggtgacatcc aatttettet gataatttag attecteaca acettectag ttaagtgaag
                                                                        240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctgc aatgaagatc
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cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga
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gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgccc
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                                                                        300
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ttottagtat tatttatggt aaataggoto ttaccacttg caaataactg gocacatcat
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taatgactga cttcccagta aggctctcta aggggtaagt angaggatcc acaggatttg
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                                                                        300
agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg
                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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<210> 266 <211> 301 <212> DNA <213> Homo sapien								
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gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc
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ttytttctgt ccagagagag tatcagtgac ananatttma gggtgaamac atgmattggt
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gggacttnty tttacngagm accetgeeg sqcqccetcq makengantt ecqesanane
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                                                                        301
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      <221> misc_feature
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tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttgtg gaaaagtcca
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tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc
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aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc
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C
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gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc
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tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag
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tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc
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agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat
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                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat
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taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc
                                                                       180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt
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aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat
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      <211> 301
      <212> DNA
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                                                                           120
gaatcatggc actectgata cttteccaaa teaacactet caatgeecca ecetegteet
                                                                           180
caccatagtg qqqaqactaa agtgqccacg gatttgcctt angtgtgcag tgcgttctga
                                                                           240
gttenetgte gattacatet gaccagtete ettttteega agteenteeg tteaatettg
                                                                           300
                                                                           301
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      <211> 301
      <212> DNA
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      <223> n = A, T, C or G
      <400> 278
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat
                                                                            60
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca
                                                                           120
cagtetetae tgttattatg cattacetgg gaatttatat aageeettaa taataatgee aatgaacate teatgtgtge teacaatgtt etggeactat tataagtget teacaggttt
                                                                           180
                                                                           240
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt
                                                                           300
                                                                           301
      <210> 279
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
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gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc
                                                                           120
ttagacettt acettecage caceccacag tgettgatat tteagagtea gteattggtt
                                                                          180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac
                                                                          240
catctqtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattqcacag
                                                                           300
                                                                          301
      <210> 280
      <211> 301
      <212> DNA
    <213> Homo sapien
      <400> 280
ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg
                                                                           60
tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct
                                                                          120
tqaqaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
                                                                          180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga
                                                                          240
cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag
                                                                          300
                                                                          301
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<210> 281
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 281
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geogageaat ecaaateetg aatgaagggg catettetga aaaaggagat etgaatetea
                                                                       120
atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa
                                                                       180
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc
                                                                       240
tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc
                                                                       300
                                                                        301
      <210> 282
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 282
caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca
                                                                        60
tocagaacco aaaaattaag aaattoaaaa agacattttg tgggcacctg ctagcacaga
                                                                       120
                                                                       180
agcgcagaag caaagcccag gcagaaccat gctaacctta cagctcagcc tgcacagaag
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg
                                                                       240
cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac aqaagcacag
                                                                       300
                                                                       301
      <210> 283
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 283
atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag
cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca
                                                                       120
gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc
                                                                       180
acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcatctttta
                                                                       240
ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttgcttt
                                                                       300
                                                                       301
      <210> 284
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 284
caggtaçaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt
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gettegtgtg tgggcaaage aacatettee etaaatatat attaccaaga aaageaagaa
                                                                       120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat
                                                                       180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt
                                                                       240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C or G
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                                                                        120
caggaaagca aatgctattt acagacetge aagecetece teaaacnaaa etatteetgg
                                                                        180
attaaatatg totgacttot tttgaggtoa cacgactagg caaatgotat ttacgatotg
                                                                        240
caaaaqctgt ttgaaqagtc aaaqccccca tgtgaacacq atttctggac cctgtaacag
                                                                        300
                                                                        301
      <210> 286
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 286
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                                                                         60
tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagatttttt
                                                                        120
atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca
                                                                        180
aaaataagct accatatagc ttataagtct caaatttttg ccttttacta aaatgtgatt
                                                                        240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg
                                                                        300
                                                                        301
      <210> 287
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 287
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                                                                        60
                                                                        120
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg
aaatgatttq gttatgaacg cacagtttag gcagcagggc cagaatcctg accetctgcc
                                                                        180
ccgtggttat ctcctccca gcttggctgc ctcatgttat cacagtattc cattttgttt
                                                                        240
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc
                                                                        300
                                                                        301
      <210> 288
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 288
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag
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aqtcaataqq aaqacaaatt ccaqttccaq ctcaqtctgg gtatctgcaa aqctgcaaaa
                                                                        120
gatetttaaa gacaatttea agagaatatt teettaaagt tggcaatttg gagateatae
                                                                       180
aaaaqcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
                                                                       240
totgoottaa ttttggatga atgoatgatg gaaattcaat aatttagaaa gttaaaaaaa
                                                                        300
                                                                       301
      <210> 289
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
      <400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgctcc tggaaactta
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gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg
                                                                       120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa
                                                                       180
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```
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaga
                                                                        240
tgtgttttgt tttggactct ctgtggtccc ttccaatgct gtgggtttcc aaccagngga
                                                                        300
а
                                                                        301
      <210> 290
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C or G
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tgactgatct gttcatitct ctcacagetc ttacccccaa aagcttttcc accctaaqtq
                                                                        120
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatq
                                                                        180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc
                                                                        240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag
                                                                        300
                                                                        301
      <210> 291
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 291
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                                                                         60
tatatcaget agatttttt tetatgettt acetgetatg gaaaatttga cacattetge
                                                                        120
tttactcttt tgtttatagg tgaatcacaa aatgtatttt tatgtattct gtagttcaat
                                                                        180
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa
                                                                        240
acatgagett cactteecca ctaactaatt ageatetgtt atttettaac eqtaatgeet
                                                                        300
                                                                        301
      <210> 292
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
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tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat qttqqtattc
                                                                        120
aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg
                                                                        180
ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc
                                                                       240
tcactacaca cacaqacccc acagtcctat atqccacaaa cacatttcca taacttqaaa
                                                                        300
а
                                                                       301
      <210> 293
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 293
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                                                                        60
ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt
                                                                       120
aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt
                                                                       180
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gtgagaattt tttaaaaggc tacttgtata ataaccettg teatttttaa tgtacetegg
                                                                        240
cogogaccae getaageega attetgeaga tateeateae aetggeggee getegageat
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                                                                        301
      <210> 294
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
      <400> 294
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attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag
                                                                        120
tttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tgaaaataag
                                                                        180
ttcactactt ttctqqqata ttctttacaa aatcttatta aaattcctqq tattatcacc
                                                                        240
cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt
                                                                        300
                                                                        301
      <210> 295
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 295
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cacatttcac tgtgatgtat attgtgttgc aaaaaaaaa gtgtctttgt ttaaaattac
                                                                        120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                        180
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatggt.
                                                                       240
totcaquacc atttcacca qacagootqt ttotatootq tttaataaat tagtttqqqt
                                                                        300
                                                                        305
tctct
      <210> 296
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 296
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                                                                        60
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg
                                                                       120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac
                                                                       180
tttqaaaaaq tqattqaacq aaccacttaq ctttcaqatq atqaacactq ataaqtcatt
                                                                       240
tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg
                                                                       300
                                                                       301
      <210> 297
      <211> 300
      <212> DNA °
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (300)
      <223> n = A, T, C or G
      <400> 297
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                                                                        60
aaqqttttga aaaccttgaa ggagaatcat tttgacaaga aqtacttaag agtctaqaqa
                                                                       120
acaaaqangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt
                                                                       180
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tocatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc
                                                                        240
accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcqq
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
      <400> 298
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ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg
                                                                        120
tgaagctctc agatcaatca cgggaagggc ctggcggtgg tggccacctq qaaccaccct
                                                                        180
gtcctgtctg tttacatttc actaycaggt tttctctggg cattacnatt tgttccccta
                                                                        240
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg
                                                                        300
      <210> 299
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 299
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                                                                        60
teactgeace etetgeetee caggttegag caatteteet geeteageet eecaggtage
                                                                        120
tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg
                                                                        180
gagtttcgcc atgttggcca gctggtctca aactcctgac ctcaagcgac ctgcctgcct
                                                                        240
cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaaqatattt
                                                                        300
                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 300
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tatgtcccac acccactggg aaaggctccc acctggctac ttcctctatc agctgggtca
                                                                       120
getgeattee acaaggitet cageetaatg agtiteacta cetgecagte teaaaactta
                                                                       180
gtaaagcaag accatgacat teeeccaegg aaateagagt ttgeeccaee gtettgttae
                                                                       240
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccgagcg catcccccat
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 301
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agaqqacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt
                                                                       120
gggaactcac aaagaccctc agagctgaga cacccacaac agtgggagct cacaaagacc
                                                                       180
ctcagagctg agacacccac aacagtggga gctcacaaag accctcagag ctgagacacc
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cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt
                                                                       300
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<210> 302 <211> 301

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      <213> Homo sapien
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                                                                       120
ttgagttggt tcttagtatt atttatggta aataggetet taccacttge aaataactgg
                                                                       180
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
                                                                       240
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccetctta ttttcagagg
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 303
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atattqtttt ttqacagttt aacacatctt cttctgtcag agattctttc acaatagcac
                                                                       120
tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc
                                                                       180
agtaacgggt atgttttict aactgatctt ttgctcgttc caaagggacc tcaagacttc
                                                                       240
categatttt atatetgggg tetaqaaaaq gagttaatet gtttteeete ataaatteae
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                                                                       301
      <210> 304
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 304
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tattagtttc agtttcagct tacccacttt ttgtctgcaa catgcaraas agacagtgcc
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ctttttagtg tatcatatca ggaatcatct cacattggtt tgtgccatta ctggtgcagt
                                                                       180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga
                                                                       240
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct
                                                                       300
                                                                       301
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    · <211> 301
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      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C or G
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                                                                        60
cagggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggcg
                                                                       120
taaaqqaqqa qaaacaqata caaaatctcc aactcaqtat taaqqtattc tcatqcctaq
                                                                       180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa
                                                                       240
ttctqqqatt taaqttggat accaangaaa ttqtattaaa aqaqctgttc atqqaataaq
                                                                       300
                                                                       301
      <210> 306
      <211> 8
      <212> PRT
      <213> Homo sapien
      <400> 306
Val Leu Gly Trp Val Ala Glu Leu
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5
 1
      <210> 307
      <211> 637
       <212> DNA
      <213> Homo sapien
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attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt
                                                                          180
cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca
                                                                          240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga
                                                                          300
gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgt
                                                                          360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa
                                                                          420
                                                                          480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca
                                                                         540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg
                                                                         600
ttacagatac tggggcagca aataaaactg aatcttg
                                                                          637
      <210> 308
      <211> 647
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (647)
      <223> n = A, T, C or G
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tgctcagggg aaggttcata tgggactttc tactgcccaa ggttctatac aggatataaa
                                                                         120
ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctq
                                                                         180
ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg
                                                                         240
ctagagaaaa gaccaacaac ggcctcaaag gatctcttac catgaaggtc tcagctaatt
                                                                         300
cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct
                                                                         360
cattttgtgt gtggataaag tcaggatgcc cagggggcag agcagggggc tgcttgcttt
                                                                         420
gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac
                                                                         480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca
                                                                         540
ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc
                                                                         600
aatgteettt ttttteteet gettetgaet tgataaaagg ggaeegt
                                                                         647
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      <211> 460
      <212> DNA
      .<213> Homo sapien
      <400> 309
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                                                                          60
aatatgattg gctgcacact tccagactga tgaatgatga acgtgatgga ctattgtatg
                                                                         120
gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc
                                                                         180
accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtccg
                                                                         240
ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag
                                                                         300,
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc
                                                                         360
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat
                                                                         420
ttgtcttgtt tttgtctttc ggtgtgtaag attcttaagt
                                                                         460
      <210> 310
      <211> 539
      <212> DNA
      <213> Homo sapien
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<400> 310
acgggactta tcaaataaag ataggaaaag aagaaaactc aaatattata ggcagaaatg
                                                                        60
ctaaaqqttt taaaatatqt caqqattqqa aqaaqqcatq qataaaqaac aaaqttcaqt
                                                                       120
taggaaagag aaacacagaa ggaagagaca caataaaagt cattatgtat tctgtgagaa
                                                                       180
gtcagacagt aagatttgtg ggaaatgggt tggtttgttg tatggtatgt attttagcaa
                                                                       240
taatctttat ggcagagaaa gctaaaatcc tttagcttgc gtgaatgatc acttgctgaa
                                                                       300
ttcctcaaqq tagqcatqat qaaqqaqqt ttagaggaga cacaqacaca atgaactgac
                                                                       360
ctagatagaa agcettagta tacteageta ggaatagtga ttetgaggge acaetgtgae
                                                                       420
atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc
                                                                       480
atattttcac ccccacaaa qtcaqttaaa tattqqqaca ctaaccatcc aggtcaaga
                                                                       539
      <210> 311
      <211> 526
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(526)
      <223> n = A, T, C or G
      <400> 311
caaatttgag ccaatgacat agaattttac aaatcaagaa gcttattctg gggccatttc
                                                                        60
ttttgacgtt ttctctaaac tactaaagag gcattaatga tccataaatt atattatcta
                                                                       120
catttacagc atttaaaatg tgttcagcat gaaatattag ctacagggga agctaaataa
                                                                       180
attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg
                                                                       240
tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa
                                                                       300
aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc
                                                                       360
tototttaca gggagotoot gcagococta cagaaatgag tggctgagat tottgattgo
                                                                       420
acagcaagag cttctcatct aaaccctttc cctttttagt atctgtgtat caagtataaa
                                                                       480
agttctataa actgtagtnt acttatttta atccccaaag cacagt
                                                                       526
      <210> 312
      <211> 500
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(500)
      <223> n = A, T, C or G
      <400> 312
cctctctctc cccacccct gactctagag aactgggttt tctcccagta ctccagcaat
teatttetga aageagttga gecaetttat tecaaagtae aetgeagatg tteaaactet
                                                                       120
                                                                       180
ccatttetet ttecetteea cetgeeagtt ttgetgaete teaacttgte atgagtgtaa
                                                                       240
gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg
gettettagg aaaatattt tetteeaaaa teagtaggaa atetaaaett ateeeetett
                                                                       300
tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct
                                                                       360
tgctaatgtg gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct
                                                                       420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt
                                                                       480
tagtcttaat tatctattgg
                                                                       500
      <210> 313
      <211> 718
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (718)
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<223> n = A, T, C or G<400> 313 ggagatttgt gtggtttgca gccgagggag accaggaaga tctgcatggt gggaaggacc 60 tgatgataca gaggtgagaa ataagaaagg ctgctgactt taccatctga ggccacacat 120 ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa 180 gtagtgacat gtttttgcac atttccagcc cttttaaata tccacacaca caggaagcac 240 aaaaqqaagc acaqaqatcc ctgggagaaa tgcccggccg ccatcttggg tcatcgatga 300 gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg 360 ttccttaaag gatggcagga aaacagatcc tgttgtggat atttatttga acgggattac 420 agatttgaaa tgaagtcaca aagtgagcat taccaatgag aggaaaacag acgagaaaat 480 cttgatggtt cacaagacat gcaacaaaca aaatggaata ctgtgatgac acgagcagcc 540 aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg 600 cgttatacca atcatttcta tttctaccct caaacaagct gtngaatatc tgacttacgg 660 ttcttntggc ccacattttc atnatccacc cententttt aannttantc caaantgt 718 <210> 314 <211> 358 <212> DNA <213> Homo sapien <400> 314 gtttatttac attacagaaa aaacatcaag acaatgtata ctatttcaaa tatatccata 60 cataatcaaa tatagctgta gtacatgttt tcattggtgt agattaccac aaatgcaagg 120 caacatgtgt agatetettg tettattett ttgtetataa taetgtattg tgtagteeaa 180 gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc 240 ttgttgtatt getgaactgt agtgeeetgt attttgette tgtetgtgaa ttetgttget 300 totggggcat ttoottqtqa tgcagaggac caccacacaq atqacaqcaa totqaatt 358 <210> 315 <211> 341 <212> DNA <213> Homo sapien <400> 315 taccacctcc ccgctggcac tgatgagccg catcaccatg gtcaccagca ccatgaaggc 60 ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcgagt 120 gacccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag ccccaatgac 180 agteaccage teccegacca geoggatate gteettaggg gteatgtagg etteetgaag 240 tagettetge tgtaagaggg tgttgteeeg ggggetegtg eggttattgg teetgggett 300 gaggggggg tagatgcagc acatggtgaa gcagatgatg t 341 <210> 316 <211> 151 <212> DNA <213> Homo sapien <400> 316 agactqqqca aqactcttac gccccacact qcaatttqqt cttqttqccq tatccattta 60 tgtgggcctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact 120 151 cattcaggga gctctggttg caatattagt t <210> 317 <211> 151 <212> DNA <213> Homo sapien <400> 317 agaactagtg gatcctaatg aaatacctga aacatatatt ggcatttatc aatggctcaa 60 atottcatti atototggco ttaaccotgg ctootgaggo tgoggcoago agatoccaqq 120 ccagggetet gttettgeea cacctgettg a 151

```
<210> 318
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 318
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gctgcaggct ggagtgtctt tattectggc gggagaccgc acattecact gctgaggctg
                                                                     120
                                                                     151
tgggggggt ttatcaggca gtgataaaca t
      <210> 319
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 319
aactagtgga tccagagcta taggtacagt gtgatctcag ctttgcaaac acattttcta
                                                                      60
catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg
                                                                     120
                                                                     151
taagattggg tttatgtgat tttagtgggt a .
      <210> 320
      <211> 150
      <212> DNA
      <213> Homo sapien
      <400> 320
aactaqtqqa tccactaqtc caqtqtqqtq qaattccatt qtqttqqqqt .tctaqatcqc
                                                                      60
120
                                                                     150
gagtgttcta cagcttacag taaataccat
      <210> 321
     <211> 151
      <212> DNA
     <213> Homo sapien
      <400> 321
                                                                      60
agcaactttg tttttcatcc aggttatttt aggcttagga tttcctctca cactgcagtt
                                                                     120
tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg
tgcctctgag aaatcaaagt cttcatacac t
                                                                     151
     <210> 322
      <211> 151
     <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(151)
     \langle 223 \rangle n = A, T, C or G
     <400> 322
atccagcatc ttctcctgtt tcttgccttc ctttttcttc ttcttasatt ctgcttgagg
                                                                     60
                                                                     120
tttgggcttg gtcagtttgc cacagggctt ggagatggtg acagtcttct ggcattcggc
attgtgcagg gctcgcttca nacttccagt t
                                                                     151
     <210> 323
     <211> 151
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
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<222> (1)...(151)
      <223> n = A, T, C or G
      <400> 323
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                                                                            60
nagactcant tactacccag tttgtggttt twtgggagaa atgtaactgg acagttagct
                                                                           120
gttcaatyaa aaagacactt ancccatgtg g
                                                                           151
      <210> 324
       <211> 461
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (461)
      <223> n = A, T, C or G
acctgtgtgg aatttcagct ttcctcatgc aaaaggattt tgtatccccg gcctacttga
                                                                            60
agaagtggtc agctaaagga atccaggttg ttggttggac tgttaatacc tttgatgaaa
                                                                           120
agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact
                                                                           180
gcgaacctca cttctagact ttcacggtgg gacgaaacgg gttcagaaac tgccaggggc ctcatacagg gatatcaaaa taccctttgt gctacccagg ccctggggaa tcaggtgact cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
                                                                           240
                                                                           300
                                                                           360
gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
                                                                           420
aaaaacgcac aagagcccct qccctqccct agctgangca c
      <210> 325
      <211> 400
      <212> DNA
      <213> Homo sapien
      <400> 325
acactgtttc catgttatgt ttctacacat tgctacctca gtgctcctgg aaacttagct
                                                                            60
tttgatqtct ccaaqtaqtc caccttcatt taactctttq aaactqtatc atctttqcca
                                                                           120
agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt
                                                                           180
totataaatg aatgtgotga agcaaagtgo coatggtggo ggogaagaag agaaagatgt
                                                                           240
gttttgtttt ggactototg tggtocotto caatgotgtg qqtttocaac caqqqqaaqq
                                                                           300
gtcccttttg cattgccaag tgccataacc atgagcacta cgctaccatg gttctgcctc
                                                                           360
ctggccaagc aggctggttt gcaagaatga aatgaatgat
                                                                           400
      <210> 326
      <211> 1215
      <212> DNA
      <213> Homo sapien
      <400> 326
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                                                                            60
gttetgeteg ggegteetgg tgeateegea gtgggtgetg teageegeae aetgttteea
                                                                           120
gaactectac accateggge tgggeetgea cagtettgag geegaecaag ageeagggag
                                                                           180
ccagatggtg gaggccagcc tctccgtacg gcacccagag tacaacagac ccttgctcgc
                                                                           240
taacgacete atgeteatea agttggacga atcegtgtee gagtetgaca ceateeggag
                                                                           300
cateageatt gettegeagt geeetaeege ggggaactet tgeetegttt etggetgggg
                                                                           360
totgotggcg aacggcagaa tgcctaccgt gctgcagtgc gtgaacgtgt cggtggtgtc
                                                                           420
tgaggaggtc tgcagtaagc tctatgaccc gctgtaccac cccagcatgt tctgcgccgg
                                                                           480
cggagggcaa gaccagaagg actcctgcaa cggtgactct ggggggcccc tgatctgcaa
                                                                           540
                                                                           600
egggtacttg cagggeettg tgtetttegg aaaageeeeg tgtggeeaag ttggegtgee
aggtgtctac accaacctct gcaaattcac tgagtggata gagaaaaccg tccaggccag
                                                                           660
ttaactctgg ggactgggaa cccatgaaat tqacccccaa atacatcctg cqqaaqqaat
                                                                           720
traggaatat ctgttcccag cocctcctcc ctcaggccca ggagtccagg cccccagccc
                                                                           780
ctecteete aaaccaaggg tacagateee cageceetee teeeteagae ecaggagtee
                                                                           840
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```
aqaccecca gecetecte ecteagacee aggagtecag eccetectee etcagaceca
qqaqtccaqa cccccaqcc cctcctccct cagacccagg ggtccaggcc cccaacccct
                                                                    960
cctccctcag actcagaggt ccaagccccc aacccctcct tccccagacc cagaggtcca
                                                                   1020
ggtcccagcc cctcctccct cagacccagc ggtccaatgc cacctagact ctccctgtac
                                                                   1080
acagtgcccc cttgtggcac gttgacccaa ccttaccagt tggtttttca ttttttgtcc
                                                                   1140
1200
                                                                   1215
aaaaaaaaa aaaaa
      <210> 327
      <211> 220
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1
Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
           20
                              25
Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
                           40
                                              45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
                       55
Ala Ser Leu Ser Val Arq His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
                                      75
                   70
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
                                  90
                                                      95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
                                                  110
           100
                              105
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
                                             125
       115
                          120
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
                      135
                                          140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
                   150
                                     155
                                                          160
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
                                                      175
                                  170
               165
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
                              185
                                                  190
           180
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
                           200
      195
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
                       215
   210
     <210> 328
     <211> 234
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     <400> 328
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agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc gtcctggtgc
                                                                    120
                                                                    180
atccqcaqtq qqtqctqtca gccacacat gtttccagaa ctcctacacc atcgggctgg
gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag gcca
                                                                    234
     <210> 329
     <211> 77
     <212> PRT
     <213> Homo sapien
     <400> 329
Leu Val Ser Gly Ser Cys Ser Gln Ile Ile Asn Gly Glu Asp Cys Ser
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Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu
             20
                                  25
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
                           40
                                                  4.5
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
    50
                        55
Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala
      <210> 330
      <211> 70
      <212> DNA
      <213> Homo sapien
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                                                                          60
gctgcagcca
                                                                          70
      <210> 331
      <211> 22
      <212> PRT
      <213> Homo sapien
      <400> 331
Gln His Asn Gly Pro Ile Pro Ser Leu Thr Pro Pro Ser Gly Ser Leu
                  5
Val Ser Gly Ser Cys Ser
            20
      <210> 332
      <211> 2507
      <212> DNA
      <213> Homo sapien
      <400> 332
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                                                                          60
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                                                                         120
                                                                         180
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                                                                         240
gggatgtgga aaagggggaa ttggtggcca aagagatcca gaccacgaca gggaaccagc
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                                                                         360
gettettage tgaggaaaag caceteeaeg ttttgateaa caatgeagga gtgatgatgt
                                                                         420
gtccgtactc gaagacagca gatggctttg agatgcacat aggagtcaac cacttgggtc
                                                                         480
acttoctoct aaccoatotg otgotagaga aactaaagga atcagcocca tcaaggatag
                                                                         540
taaatgtgtc ttccctcgca catcacctgg gaaggatcca cttccataac ctgcagggcg
                                                                         600
agaaattota caatgoaggo otggootaet gtoacagoaa gotagooaac atcotottoa
                                                                         660
cccaggaact ggcccggaga ctaaaaggct ctggcgttac gacgtattct gtacaccctq
                                                                         720
gcacagtcca atctgaactg gttcggcact catctttcat gagatggatg tggtggcttt
                                                                         780
totoottttt catcaagact cotcagoagg gagoocagao cagootgoac tgtgoottaa
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cagaaggtet tgagatteta agtgggaate attteagtga etgteatgtg geatgggtet
                                                                         900
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                                                                        1380
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agggagtatt ttcacaaagt tcaaaacagc cacaataatc agagatggag caaaccagtg

PCT/US00/27464

2400

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1800

1860

1920

1980

2000

## 114

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115

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                                                                         1140
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                                                                         1800
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Glu Tyr Thr Ile Val His Ala Ser Phe Ile Ser Cys Ile Ser Ser Ser
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                                                 45
Leu Asp Gly Gln Gly Glu Arg Gln Glu Gln Arg Gly His Phe Trp Arg
                        55
Pro Gln Arg Leu Cys Glu Asp Ala Trp Glu Gln Glu Val Gln Val
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Val Leu Pro Leu Leu Pro Leu Leu Gln Gly Ser Gly Lys Ser Asn Val
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Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr
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105

His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp

110

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Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp
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Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Cys
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                           170
Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala
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Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly
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Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr
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Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr 225 230 235 240
Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu
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Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys
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                                          270
Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu
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Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu
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Ser Met Leu Phe Leu Val Ile Ile Met
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Lys Asn Lys Val

145

<400> 377

117

## <213> Homo sapien

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465					470					475					480
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	Arg		500				_	505			_	_	510		_
Asp	Ser	Ala 515	Phe	Met	Glu	Pro	Arg 520	Tyr	His	Val	Arg	Gly 525	Glu	Asp	Leu
Asp	Lys 530	Leu	His	Arg	Ala	Ala 535	Trp	Trp	Gly	Lys	Val 540	Pro	Arg	Lys	Asp
Leu 545	Ile	Val	Met	Leu	Arg 550	Asp	Thr	Asp	Val	Asn 555	Lys	Lys	Asp	Lys	Gln 560
Lys	Arg	Thr	Ala	Leu 565	His	Leu	Ala	Ser	Ala 570	Asn	Gly	Asn	Ser	Glu 575	Val
	Lys		580				_	585					590	_	
_	Lys	595					600					605		_	
	Ala 610					615	•				620				_
625	Tyr				630			_		635	_			_	640
	Met -			645					650		_			655	_
	Lys		660					665					670		_
	Gln	675					680					685			
	Asp 690				_	695					700		_	-	_
705	Ala				710					715					720
	Gln			725					730					735	
	His		740					745					750		
	Leu	755					760					765			_
	Thr 770					775					780				
785	Pro Glu				790					795		-	_	_	800
	Leu			805					810					815	
	Leu		820					825			_		830	_	
	Asp	835					840					845			
	850 Tyr					855	_		_		860				
865	Glu	_		_	870			_	_	875					880
	Gly			885	_				890					895	
	Glu		900					905					910		
	Thr	915	_	_		_	920				-	925			
	930 Arg					935					940	_			
945	Glu				950					955			_		960
22011	J_4	J_ U	- 1 -				J_ u			-10	****		-y 3	3111	T 11G

119

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1460 1465 1470 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly 1475 . 1480 1485 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu 1495 1500 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys 1505 1510 1515 152 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser 1525 1530 1535Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu 1540 1545 1550 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser 1555 1560 1565 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe 1570 1575 1580 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe 1585 1590 1595 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly 1605 1610 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro 1625 1620 1630 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln 1635 1640 1645 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile 1650 1655 1660 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser 1665 1670 1675 168 Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn 1685 1690 1695 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr 1700 1705 Met Lys His Gln Ser Gln Leu 1715

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<211> 656

<212> PRT

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<400> 379

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Leu	His	Leu	Ala 180		Ala	Asn	Gly	Asn 185		Glu	Val	Val	Lys 190	Leu	Leu
Leu	Asp	Arg 195	Arg	Cys	Gln	Leu	Asn 200	Val	Leu	Asp	Asn	Lys 205		Arg	Thr
Ala	Leu 210	Ile	Lys	Ala	Val	Gln 215	_	Gln	Glu	Asp	Glu 220	_	Ala	Leu	Met
Leu 225	Leu	Glu	His	Gly	Thr 230		Pro	Asn	Ile	Pro 235	Asp	Glu	Tyr	Gly	Asn 240
			His	245			_		250	_	_			255	-
			Leu 260	_	_		_	265					270		
		275					280					285			
_	290		Ile			295					300	•			
305	-		Ala		310					315	_				320
			Leu Thr	325					330					335	
	_		340 Leu					345					350		
	-	355	Asn			-	360	_		_		365		_	
	370		Gln			375	,				380				
385			Glu	•	390	_	_			395					400
Glu	Glu	Met	Lys	405 Lys	His	Glu	Ser	Asn	410 Asn	Val	Gly	Leu	Leu	415 Glu	Asn
T	mъ	7	420	1703	mb w	71.	C1	425	C1	7.00	7.00	C1	430	T10	Dwa
		435	Gly Ser				440		•			445			
	450		Tyr			455					460				
465			_		470		_			475		_	_	_	480
_			Pro	485	_				490					495	
	-		Thr 500					505		_			510		
		515	Pro				520					525			
-	530	_	Ser			535	_				540				_
545	Thr	Ата	Gly	ASI	550	Asp	Asp	ста	ren	555	Pro	Pro	Arg	гуѕ	560
-			Glu	565					570					575	
		-	Glu 580			_		585	-			_	590		
		595	Ile			_	600					605		_	
	610		Val -		-	615					620			-	-
625		•	Asp -		630					635		_			640
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123

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Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
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aagestatgg coagetgtet ttgtgtteee teteaceege etgteeteae agetgagaet 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
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getetangag tetganenga ntegttgeee cantntgaca naaggaaagg eggagettat 180
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naantingat niceanagee claeceaten tagtietget eleccaeegg niaeeageee 240
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<400> 401
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tgatgtctcc aaqtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300
cccttttgca ttgccaaqtq ccataaccat qaqcactact ctaccatgqn tctgc
<210> 402
<211> 407
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc feature
<222> (1) ... (407)
<223> n = A, T, C or G
<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60
teteacatge ggtggcatae ataggeteaa aataaaggaa tggagaaaaa tattteaage 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggaget teteceetge agagagteee tgateteeca aaatttggtt gagatgtaaq 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (303)
<223>.n = A,T,C or G
<400> 403
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcaccaaa 60
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatqq 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tettaacaae gacegaaaee cattatttae ataaaeetee atteggtaae catgttgaaa 300
gga
                                                                   303
<210> 404
<211> 225
<212> DNA
<213> Homo sapiens
<400> 404
aagtgtaact tttaaaaatt tagtggattt tgaaaattct tagaqgaaaq taaaggaaaa 60
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
<210> 405
<211> 334
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(334)
<223> n = A, T, C or G
<400> 405
gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctcccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
teatececat eccatgeeaa aggaagaeee teeteettg geteacagee ttetetagge 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
etggtgeggt tgtgeeteea gettetgete agtgetteat ggaeagtgte eageceatgt 300
cactetecac teteteanng tggateceae eect
                                                                   334
```

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<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A, T, C or G
<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatqt tqcacccttq tttctacacc tqtqqqttat qacaaaqaca 180
actgccaaag aatnttcaag aaggaggact gccant
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
getgaettge tagtateate tgeatteatt gaageacaag aactteatge ettgaeteat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
cccaqaqqtc tatqtcctaa tqtqttatqq caaatqgatq tcatqcacqt accttcattt 240
ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag
<210> 408
<211> 183
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(183)
<223> n = A, T, C or G
<400> 408
ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tnottaacta qttaatoott aaagggotan ntaatootta actagtooot coattgtgag 120
cattateett ecagtatten cettetnttt tatttaetee tteetggeta eccatgtaet 180
ntt
<210> 409
<211> 250
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (250)
<223> n = A, T, C or G
<400> 409
cccacqcatq ataaqctctt tatttctqta aqtcctqcta qqaaatcatc aaatctqacq 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
qcttcccaqt qcccccaqqa caqcqtqqqc tatqtttaca qcqcntcctt qctqqqqqq 240
ggccntatgc
```

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<210> 410
<211> 306
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (306)
<223> n = A, T, C or G
<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtettgeaa teccatttge aggateegte tgtgeacatg cetetgtaga gageageatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttcct tctttattqc cccttcttat ttatqtqaac 240
nactggttgg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
tcntgc
<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (261)
<223> n = A, T, C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatettttg tatttaagga ttetgagatt ttgettgage aggattagat aaggetgtte 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (241)
\langle 223 \rangle n = A,T,C or G
<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggagggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(231)
<223> n = A, T, C or G
```

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<400> 413 aactettaca atecaagtga eteatetgtg tgettgaate ettteeactg teteatetee 60 ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120 aagtttactc tecteatttq gaacetaaaa actetettet teetgggtet gagggeteea 180 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t <210> 414 <211> 234 <212> DNA <213> Homo sapiens <400> 414 actifticate aagcacteae cagaagctee agcacaace caccagacac tcacagcaae 60 gatggagetg aaaacataac ccactetgte etggaggeac tgggaageet agagaagget 120 gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180 ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca <210> 415 <211> 217 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1) ... (217) <223> n = A, T, C or G<400> 415 gcataggatt aagactgagt atcttttcta cattettta actttctaag gggcacttct 60 caaaacacaq accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120 cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180 antggattat aaaaaataac aattaagaaa aataatc <210> 416 <211> 213 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1) ... (213) <223> n = A, T, C or G<400> 416 atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60 ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120 cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180 atattggaac agatggagtc tctactacaa aag <210> 417 <211> 303 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1)...(303) <223> n = A,T,C or G <400> 417 nagtetteag geceateagg gaagtteaca etggagagaa gteatacata tgtaetgtat 60

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gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaaq 180
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
<210> 418
<211> 328
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(328)
<223> n = A, T, C or G
<400> 418
tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacacca qctagttttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
teagnggtea ggetggtete aaacteetga eeteaagtga tetgeecace teageeteec 300
aaagtgctan gattacaggc cgtgagcc
<210> 419
<211> 389
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(389)
<223> n = A, T, C or G
<400> 419
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
acccctgage catggactgg agectgaaag geagegtaea eeetgeteet gatettgetg 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactqaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt gtgccaggca 240
coggttotec agocaccaac ctcactogot coogcaaatg goacatoagt tottotacco 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg
<210> 420
<211> 408
<212> DNA
<213> Homo sapiens
<400> 420
gttectecta actectgeca gaaacagete tecteaacat gagagetgea eccetectee 60
tggccagggc agcaagcett agcettgget tettgtttet gettittte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccq
                                                                   408
<210> 421
<211> 352
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1) ... (352)
<223> n = A, T, C or G
<400> 421
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggict tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
qqtqcaacat qaaatttctq tttcqtagca aqtqcatqtc tcacaagttg qcanqtctgc 300
cacteegagt ttattgggtg tttgttteet ttgagateea tgeattteet gg
<210> 422
<211> 337
<212> DNA
<213> Homo sapiens
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
qtqaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atcogacaco ggtgcacotg gaagcottgc agoggotggg googacgcog attoacogac 300
gcttcttccg ccggtacggc tggcctatga aaattat
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A, T, C \text{ or } G
<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
teactgacag aacaggtett ttttgggtee ttetteteea ceacgatata ettgeagtee 180
teettettga agattetttg geagttgtet ttgteataac ceacaggtgt anaaacaagg 240
gtgcaacatg aaatttetgt ttegtageaa gtgcatgtet cacagttgte aagtetgeee 300
tccgagttta
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A, T, C or G
<400> 424
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
cactgacaga acaggictit titigggicct tettetecae cacgatatae tigeagteet 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240
ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacqaaqqtq qcaaaqatca caacqctqcc caqqanaaca ttcattqtqa taaqcaggac 360
tccgtcgacg
```

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<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(216)
<223> n = A, T, C or G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
anattateca ttainttaag ggttgactte aggntacage acacagacaa acatgeecag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
                                                                 216
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct
                                                               596
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(107)
<223> n = A, T, C \text{ or } G
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
                                                                107
<210> 428
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (38)
<223> n = A, T, C or G
<400> 428
gaacttccna anaangactt tattcactat tttacatt
                                                                38
<210> 429
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<211> 544
<212> DNA
<213> Homo sapiens
<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagage ggetgeagee etgeggttea gattaaaate egagaattgt atagacgeeg 120
atatccacga actettgaag gactttetga tttatccaca atcaaatcat eggtttteag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctcactcacc atcctctcct gttggttctg tgctgcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tqatqtqcaq ttaaaaaatc tqccctttta tqatqtcctt gatqttctca tcaagcccac 420
qaqtttaqtt caaagcagta ticagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(507)
<223> n = A, T, C or G
<400> 430
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
gaacactgac acccatcttc caccccgaca ctctgattta attgggctgc agtgagaaca 120
qaqcatcaat ttaaaaaqct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
ccttcqtqac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaagat 480
ttttqaqcaa aaaaaaaaa aaaaaaa
<210> 431
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
<223> n = A, T, C or G
<400> 431
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaaqaaa qcacttatca qqaqqactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
qcaatgagtc tggcttttac tctgctgttt ct
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
<220>
```

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<221> misc\_feature <222> (1) ... (387) <223> n = A, T, C or G<400> 432 ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60 aaatgcaagg caacatgtgt agatetettg tettattett ttgtetataa taetgtattg 120 ngtagtecaa geteteggna gtecagecae tgngaaacat geteeettta gattaacete 180 gtggacnetn ttgttgnatt gtetgaactg tagngeeetg tattttgett etgtetgnga 240 attetgttge ttetggggea ttteettgng atgeagagga ceaccacaca gatgacagea 300 atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360 acaacgtata gaacactgga gtccttt <210> 433 <211> 281 <212> DNA <213> Homo sapiens <221> misc feature <222> (1)...(281) <223> n = A, T, C or G<400> 433 ttcaactage anagaanact gettcagggn gtgtaaaatg aaaggettee acgeagttat 60 ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120 caggenetat ttgggttgge tggaggaget gtggaaaaca tggagagatt ggegetggag 180 ategeogtgg ctattecten ttgntattae accagngagg ntetetgtnt geceactggt 240 tnnaaaaccg ntatacaata atgatagaat aggacacaca t <210> 434 <211> 484 <212> DNA <213> Homo sapiens <400> 434 ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60 aatttaattc titcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120 tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180 tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240 agctagtcta tcagcatctg acaggtgaat tggatggttc tcagaaccat ttcacccaga 300 cagoctgttt ctatoctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360 tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420 tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480 ttta <210> 435 <211> 424 <212> DNA <213> Homo sapiens <400> 435 gegeegetea gageaggtea etttetgeet tecaegteet cetteaagga ageeceatgt 60 gggtagettt caatategea ggttettaet eetetgeete tataagetea aacceaceaa 120 cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180 atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240 cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300 ggtagagacc tttgggggtc tggaacctct ggactececa tgctctaact eccacactet 360 gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420 aaac

<210> 436

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<211> 667
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G
<400> 436
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tectggeeat gtaateetga aagtttteee aaggtageta taaaateett ataagggtge 120
agoctottot ggaattooto tgatttoaaa gtotoactot caagttottg aaaacgaggg 180
cagtteetqa aaqqeaqqta tagcaactga tetteagaaa gaggaactgt gtgcaecggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
qccaqqtttq tcataqcact catcaaaqtc cqqtcaacqt ctqtqcttcq aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gatteettta tggggteagt gggaaaggtg teaatgggae tteggtetee atgeegaaac 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag
<210> 437
<211> 693
<212> DNA
<213> Homo sapiens
<400> 437
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacaqccaq qtaaqqaaaq ctggattggc acactaggac tctaccatac cgggttttgt 120
taaaqctcaq qttaqqaqqc tqataaqctt ggaaggaact tcagacagct ttttcagatc 180
ataaaagata attettagee catgttette tecagageag acetgaaatg acageacage 240
aggtactect ctattttcac coetettget tetactetet ggcagtcaga cetgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
cattleteca ggttacceta ggtgtcacta ttggggggac agccagcate tttagettte 420
atttqaqttt ctqtctqtct tcaqtaqaqq aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tectatttet aggeaetqaq qgetgtgggg tacettgtgg tgecaaaaca gateetgttt 600
taaqqacatq ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
ctgcttatca caatgaatgt teteetggge agegttgtga tetttgeeae ettegtgaet 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atqtttctac acctgtqqqt tatqacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
qcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> (1)...(431)
<223> n = A,T,C or G
<400> 439
gttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagectt agecttggct tettgtttet getttttte tggctagaec 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t
<210> 440
<211> 523
<212> DNA
<213> Homo sapiens
<400> 440
agagataaag ettaggteaa agtteataga gtteeeatga aetatatgae tggeeacaea 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctqttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta
                                                                     523
<210> 441
<211> 430
<212> DNA
<213> Homo sapiens
<400> 441
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaageett ageettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag tigaagtitg tgactitggt gitteggeat ggagaeegaa 180 gteecattga cacettteec aetgaeecca taaaggaate eteatggeea caaggatitg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt egaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag
                                                                     430
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
<400> 442
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctggaa tgacaattat attttaactt tggtggggga aagagttata ggaccacagt 120
cttcacttct gatacttqta aattaatctt ttattqcact tqttttqacc attaaqctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
                                                                    362
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (1)...(624)
<223> n = A, T, C or G
<400> 443
tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60
ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180
tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360
taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420
atggtaaaca teettattat taaagteaac getaaaatga atgtgtgtge atatgetaat 480
agtacagaga qaqqqcactt aaaccaacta aqqqcctqqa qqqaaqqttt cctqqaaaga 540
ngatgettgt getgggteca aatettggte tactatgace ttggccaaat tatttaaact 600
ttgtccctat ctgctaaaca gatc
<210> 444
<211> 425
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (425)
<223> n = A, T, C or G
<400> 444
gcacatcatt nntcttgcat tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
gaagetttgt ceaggeetgt gtgtgaacce aatgttttge ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
cetetgeaat etgecacete etgetggeag gatttgtttt tgeateetgt gaagageeaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga
<210> 445
<211> 414
<212> DNA
<213> Homo sapiens
<221> misc feature
<222> (1)...(414)
<223> n = A,T,C or G
<400> 445
catgtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatqqccaqa qtctcaacaa actgtatctt caagtctttg 120
tgaaattott tgcatgtggc agattattgg atgtagtttc ctttaactag catataaatc 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatoctacto acaaatgact aggottotoo tottgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag
<210> 446
<211> 631
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc_feature
<222> (1)...(631)
<223> n = A, T, C or G
<400> 446
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60
tetgeatgea tgggaagtgt gageatteta teaatatgea ggageeatet tgeaggtgtq 120
atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
coggtoctgt acgatiticag tatgicttaa togcagotgt gattggaaca attoagattg 240
ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300
actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420 taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccttg catttgtggt 540
aatctacacc aatgaaaaca tgtactacag ctatatttqa ttatgtatqq atatatttqa 600
aatagtatac attgtcttga tgttttttct g
<210> 447
<211> 585
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(585)
<223> n = A, T, C or G
<400> 447
ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60
cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120
gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
agtteetgaa aggeaggtat ageaactgat etteagaaag aggaactgtg tgeaceggga 240
tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300
ccaggtttgt catagoactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
gttcataatg ctgctccatg cccaqctggg tgagttqqcc aaatccttqt qqccatqaqq 480
attectttat ggggteagtg ggaaaggtgt caatgggaet teggteteea tgeegaaaca 540
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta
<210> 448
<211> 93
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (93)
\langle 223 \rangle n = A, T, C or G
<400> 448
tgetegtggg teattetgan nneegaaetg acentgeeag eeetgeegan gggeeneeat 60
ggeteectag tgeectggag aggangggge tag
                                                                      93
<210> 449
<211> 706
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> (1)...(706) <223> n = A, T, C or Gccaagttcat gctntgtgct ggacgctgga cagggggcaa aagcnnttgc tcgtgggtca 60 ttctqancac cqaactqacc atqccaqccc tqccqatggt cctccatqqc tccctaqtqc 120 cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180 cggggacage atoctgcaga tggtcgggcg cgtcccattc gccattcagg ctgcgcaact 240 gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300 gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcncga cgttgtaaaa 360 cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcatgcacg 420 cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480 cqacqtqqqa tccncactqa qaqaqtqqaq aqtqacatqt gctqqacnct qtccatqaaq 540 cactgageag aagetggagg cacaacgene cagacactea cagetactea ggaggetgag 600 aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660 qcatggatga cagagtgaaa ctccatctta aaaaaaaaa aaaaaa <210> 450 <211> 493 <212> DNA <213> Homo sapiens <400> 450 gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60 acaqttttaa aaggtaaaac aacataaaaa gaaatateet atagtggaaa taagagagte 120 aaatgagget gagaacttta caaagggate ttacagacat gtegecaata teactgeatg 180 aqcctaaqta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240 caagtcaggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300 agagacactg toagagagtt aaaaagtgag ttotatocat gaggtgatto cacagtotto 360 tcaaqtcaac acatctqtqa actcacaqac caaqttctta aaccactqtt caaactctqc 420 tacacatcag aatcacctgg agagetttac aaacteecat tgeegagggt egaegeggee 480 gcgaatttag tag 493 <210> 451 <211> 501 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> (1) ... (501) <223> n = A,T,C or G<400> 451 qqqcqcqtcc cattcqccat tcaggctqcq caactqttqq qaaqqqcqat cqqtqcqqqc 60 ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120 aacqccaqqq ttttcccaqt cncqacqttq taaaacqacq qccaqtqaat tgaatttaqq 180 tgacnetata gaagagetat gaegtegeat geaegegtae gtaagettgg ateetetaga 240 geggeegect actactacta aattegegge egegtegaeg tgggateene aetgagagag 300 tggagagtga catgtgctgg acnetgteea tgaageactg ageagaaget ggaggeacaa 360 cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420 gttgcaatga gctgagatca ggccnctgcn ccccagcatg gatgacagag tgaaactcca 480 tcttaaaaaa aaaaaaaaa a <210> 452 <211> 51 <212> DNA <213> Homo sapiens

<220>

<221> misc\_feature <222> (1)...(51)

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<223> n = A, T, C or G
<400> 452
agacggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c
                                                                      51
<210> 453
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(317)
<223> n = A, T, C or G
<400> 453
tacatettge tttttcccca ttggaactag tcattaacce atetetgaac tggtagaaaa 60
acatctgaag agctagteta teageatetg geaagtgaat tggatggtte teagaaceat 120 tteacecana cageetgtt etateetgtt taataaatta gtttgggtte tetacatgea 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccaccaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
tacccatgtc tttatta
                                                                      317
<210> 454
<211> 231
<212> DNA
<213> Homo sapiens
<400> 454
ttcgaggtac aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60
taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
agaagaccaa attettetge ateccagett geaaacaaaa ttgttettet aggteteeac 180
ccttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t
<210> 455
<211> 231
<212> DNA
<213> Homo sapiens
<400> 455
taccaaagag ggcataataa tcagtctcac agtagggttc accatcctcc aagtgaaaaa 60
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact tetecaagga tetteetttg gcategacca cattcagggg 180
caaagaattt ctcatagcac agctcacaat acagggctcc tttctcctct a
<210> 456
<211> 231
<212> DNA
<213> Homo sapiens
<400> 456
ttggcaggta cccttacaaa gaagacacca taccttatgc gttattaggt ggaataatca 60
ttccattcag tattatcgtt attattcttg gagaaaccct gtctgtttac tgtaaccttt 120
tgcactcaaa ttcctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tggtgcagct gctagtcagt ccctgactga cattgccaag t
<210> 457
<211> 231
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> (1) ... (231)
<223> n = A, T, C or G
<400> 457
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gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120
tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g
<210> 458
<211> 231
<212> DNA
<213> Homo sapiens
<400> 458
aggtctggtt cccccactt ccactccct ctactctctc taggactggg ctgggccaag 60
aqaaqaqqqq tqqttaqqqa aqccqttqaq acctqaaqcc ccaccctcta ccttccttca 120
acaccctaac cttqqqtaac aqcatttqqa attatcattt qqqatqaqta qaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t
<210> 459
<211> 231
<212> DNA
<213> Homo sapiens
<400> 459
qqtaccqaqq ctcqctqaca caqaqaaacc ccaacqcqaq gaaaggaatg gccaqccaca 60
cettegegaa acetgtggtg geceaceagt cetaacggga caggacagag agacagagca 120
geoetgeact gtttteecte caccacagee atcetgteec teattggete tgtgetttee 180
actatacaca qtcaccqtcc caatqaqaaa caaqaaqqaq caccctccac a
<210> 460
<211> 231
<212> DNA
<213> Homo sapiens
<400> 460
gcaggtataa catgctgcaa caacagatgt gactaggaac ggccggtgac atggggaggg 60
cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagettg gtecageete eagteeacee etaceagget taaggataga a
<210> 461
<211> 231
<212> DNA
<213> Homo sapiens
cgaggtttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggagggtc 60
gcgtgtgctc cagaagagtg tgtgcatgcc agaggggaaa caggcgcctg tgtgtcctgg 120
gtggggttca gtgaggagtg ggaaattggt tcagcagaac caagccgttg ggtgaataag 180
agggggattc catggcactg atagagccct atagtttcag agctgggaat t
<210> 462
<211> 231
<212> DNA
<213> Homo sapiens
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147

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152

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153

130

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Gln 65	_	Val	Leu	Thr	Ala 70	Ala	His	Суз	Ile	Arg 75	Asn	Lys	Ser	Val	Ile 80
Leu	Leu	Gly	Arg	His 85	Ser	Leu	Phe	His	Pro 90	Glu	Asp	Thr	Gly	Gln 95	Val
Phe	Gln	Val	Ser 100	His	Ser	Phe	Pro	His 105	Pro	Leu	Туг	Asp	Met 110		Leu
Leu	Lys	Asn 115	Arg	Phe	Leu	Arg	Pro 120	Gly	Asp	Asp	Ser	Ser 125	His	Asp	Leu
Met	Leu 130	Leu	Arg	Leu	Ser	Glu 135	Pro	Ala	Glu	Leu	Thr 140	Asp	Ala	Val	Lys
Val 145	Met	Asp	Leu	Pro	Thr 150	Gln	Glu	Pro	Ala	Leu 155	Gly	Thr	Thr	Суз	Tyr 160
Ala	Ser	Gly	Trp	Gly 165	Ser	Ile	Glu	Pro	Glu 170	Glu	Phe	Leu	Thr	Pro 175	Lys
Lys ·	Leu	Gln	Cys 180	Val	Asp	Leu	His	Val 185	Ile	Ser	Asn	Asp	Val 190	Cys	Ala
Gln	Val	His 195	Pro	Gln	Lys	Val	Thr 200	Lys	Phe	Met	Leu	Cys 205	Ala	Gly	Arg
Trp	Thr 210	Gly	Gly	Lys	Ser	Thr 215	Cys	Ser	Gly	Asp	Ser 220	Gly	Gly	Pro	Leu
Val 225	Cys	Asn	Gly	Val	Leu 230	Gln	Gly	Ile	Thr	Ser 235	Trp	Gly	Ser	Glu	Pro 240
Cys	Ala	Leu	Pro	Glu 245	Arg	Pro	Ser	Leu	Tyr 250	Thr	Lys	Val	Val	His 255	Tyr
Arg	Lys	Trp	Ile 260	Lys	Asp	Thr	Ile	Val 265	Ala	Asn	Pro	Gly	Ser 270	Met	Ala
Thr	Ala	Gly 275	Asn	Pro	Trp	Gly	Trp 280	Phe	Leu	Gly	Tyr	Leu 285	Ile	Leu	Gly
Val	Ala 290	Gly	Ser	Leu	Val	Ser 295		Ser	Cys	Ser	Gln 300	Ile	Ile	Asn	Gly
Glu 305	Asp	Суѕ	Ser	Pro	His 310	Ser	Gln	Pro	Trp	Gln 315	Ala	Ala	Leu	Val	Met 320
Glu	Asn	Glu	Leu	Phe 325	Cys	Ser	Gly	Val	Leu 330	Val	His	Pro	Gln	Trp 335	Val
Leu	Ser	Ala	Ala 340	His	Cys	Phe	Gln	Asn 345	Ser	Tyr	Thr	Ile	Gly 350	Leu	Gly
Leu	His	Ser 355	Leu	Glu	Ala	Asp	Gln 360	Glu	Pro	Gly	Ser	Gln 365	Met	Val	Glu
Ala	Ser 370	Leu	Ser	Val	Arg	His 375	Pro	Glu	Tyr	Asn	Arg 380	Pro	Leu	Leu	Ala

Asn 385	Asp	Leu	Met	Leu	Ile 390	Lys	Leu	Asp	Glu	Ser 395	Val	Ser	Glu	Ser	Asp 400
Thr	Ile	Arg	Ser	Ile 405	Ser	Ile	Ala	Ser	Gln 410	Cys	Pro	Thr	Ala	Gly 415	Asn
Ser	Cys	Leu	Val 420		Gly	Trp	Gly	Leu 425	Leu	Ala	Asn	Gly	Arg 430	Met	Pro
Thr	Val	Leu 435	Gln	Суѕ	Val	Asn	Val 440	Ser	Val	Val	Ser	Glu 445	Glu	Val	Cys
Ser	Lys 450	Leu	Tyr	Asp	Pro	Leu 455	Tyr	His	Pro	Ser	Met 460	Phe	Cys	Ala	Gly
Gly 465	Gly	Gln	Asp	Gln	Lys 470	Asp	Ser	Cys	Asn	Gly 475	Asp	Ser	Gly	Gly	Pro 480
Leu	Ile	Cys	Asn	Gly 485	Tyr	Leu	Gln	Gly	Leu 490	Val	Ser	Phe	Gly	Lys 495	Ala
Pro	Cys	Gly	Gln 500	Val	Gly	Val	Pro	Gly 505	Val	Tyr	Thr	Asn	Leu 510	Суѕ	Lys
Phe	Thr	Glu 515	Trp	Ile	Glu	Lys	Thr 520	Val	Gln	Ala	Ser	Glu 525	Phe	Met	Val
Gln	Arg 530	Leu	Trp	Val	Ser	Arg 535	Leu	Leu	Arg	His	Arg 540	Lys	Ala	Gln	Leu
Leu 545	Leu	Val	Asn	Leu	Leu 550	Thr	Phe	Gly	Leu	Glu 555	Val	Суѕ	Leu	Ala	Ala 560
Gly	Ile	Thr	Tyr	Val 565	Pro	Pro	Leu	Leu	Leu 570	Glu	Val	Gly	Val	Glu 575	Glu
Lys	Phe	Met	Thr 580	Met	Val	Leu	Gly	Ile 585	Gly	Pro	Val	Leu	Gly 590	Leu	Val
Cys	Val	Pro 595	Leu	Leu	Gly	Ser	Ala 600	Ser	Asp	His	Trp	Arg 605	Gly	Arg	Tyr
Gly	Arg 610	Arg	Arg	Pro	Phe	Ile 615	Trp	Ala	Leu	Ser	Leu 620	Gly	Ile	Leu	Leu
Ser 625	Leu	Phe	Leu	Ile	Pro 630	Arg	Ala	Gly	Trp	Leu 635	Ala	Gly	Leu	Leu	Cys 640
Pro	Asp	Pro	Arg	Pro 645	Leu	Glu	Leu	Ala	Leu 650	Leu	Ile	Leu	Gly	Val 655	Gly
Leu	Leu	Asp	Phe 660	Cys	Gly	Gln	Val	Cys 665	Phe	Thr	Pro	Leu	Glu 670	Ala	Leu
Leu	Ser	Asp 675	Leu	Phe	Arg	Asp	Pro 680	Asp	His	Cys	Arg	Gln 685	Ala	Tyr	Ser
Val	Tyr 690	Ala	Phe	Met	Ile	Ser 695	Leu	Gly	Gly	Cys	Leu 700	Gly	Tyr	Leu	Leu
Pro	Ala	Ile	Asp	Trp	Asp	Thr	Ser	Ala	Leu	Ala	Pro	Tyr	Leu	Gly	Thr

703					/10					/13					120
Gln	Glu	Glu	Cys	Leu 725	Phe	Gly	Leu	Leu	Thr 730	Leu	Ile	Phe	Leu	Thr 735	Cys
Val	Ala	Ala	Thr 740	Leu	Leu	Val	Ala	Glų 745	Glu	Ala	Ala	Leu	Gly 750	Pro	Thr
Glu	Pro	Ala 755	Glu	Gly	Leu	Ser	Ala 760	Pro	Ser	Leu	Ser	Pro 765	His	Cys	Cys
Pro	Cys 770	Arg	Ala	Arg	Leu	Ala 775	Phe	Arg	Asn	Leu	Gly 780	Ala	Leu	Leu	Pro
Arg 785	Leu	His	Gln	Leu	Cys 790	Суз	Arg	Met	Pro	Arg 795	Thr	Leu	Arg	Arg	Leu 800
Phe	Val	Ala	Glu	Leu 805	Суѕ	Ser	Trp	Met	Ala 810	Leu	Met	Thr	Phe	Thr 815	Leu
Phe	Tyr	Thr	Asp 820	Phe	Val	Gly	Glu	Gly 825	Leu	Tyr	Gln	Gly	Val 830	Pro	Arg
Ala	Glu	Pro 835	Gly	Thr	Glu	Ala	Arg 840	Arg	His	Tyr	Asp	Glu 845	Gly	Val	Arg
Met	Gly 850	Ser	Leu	Gly	Leu	Phe 855	Leu	Gln	Суѕ	Ala	Ile 860	Ser	Leu	Val	Phe
Ser 865	Leu	Val	Met	Asp	Arg 870	Leu	Val	Gln	Arg	Phe 875	Gly	Thr	Arg	Ala	Val 880
Tyr	Leu	Ala	Ser	<b>Val</b> 885	Ala	Ala	Phe	Pro	Val 890	Ala	Ala	Gly	Ala	Thr 895	Cys
Leu	Ser	His	Ser 900	Val	Ala	Val	Val	Thr 905	Ala	Ser	Ala	Ala	Leu 910	Thr	Gly
Phe	Thr	Phe 915	Ser	Ala	Leu	Gln	Ile 920	Leu	Pro	Tyr	Thr	Leu 925	Ala	Ser	Leu
Гуr	His 930	Arg	Glu	Lys	Gln	Val 935	Phe	Leu	Pro	Lys	Tyr 940	Arg	Gly	Asp	Thr
Gly 945	Gly	Ala	Ser	Ser	Glu 950	Asp	Ser	Leu	Met	Thr 955	Ser	Phe	Leu	Pro	Gly 960
Pro	Lys	Pro	Gly	Ala 965	Pro	Phe	Pro	Asn	Gly 970	His	Val	Gly	Ala	Gly 975	Gly
Ser	Gly	Leu	Leu 980	Pro	Pro	Pro	Pro	Ala 985	Leu	Cys	Gly	Ala	Ser 990	Ala	Cys
Asp	Val	Ser 995	Val	Arg	Val	Val	Val 1000		Glu	Pro	Thr	Glu 100		Arg	Val
/al	Pro 1010	_	Arg	Gly	Ile	Cys 101	_	Asp	Leu	Ala		Leu 20	Asp	Ser	Ala
Phe 1025		Leu	Ser	Gln	Val 103	Ala 0	Pro	Ser	Leu		Met	Gly	Ser	Ile	Val 104

Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala Gly Leu  $1045 \hspace{1cm} 1050 \hspace{1cm} 1055$ 

Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp Lys Ser 1060 1065 1070

Asp Leu Ala Lys Tyr Ser Ala 1075